THE EARLY PROGNOSIS OF EPILEPSY

R. D. C. Elwes BSc(Hons), MB ChB, MRCP

MD Thesis

University of Edinburgh

1988

ACKNOWLEDGMENTS

The patients studied in this thesis all attended the Neurology Department at Kings College Hospital, London under the care of Dr E. H. Reynolds. The experimental work was carried out under his close supervision and I am extremely gratefull to him for all the direction and guidance he has given me. I am also deeply indebted to Dr Reynolds, not only for what he has taught me about the care of patients with epilepsy, but also for his subsequent support and the constant help and encouragement he has given me in the preparation of this thesis.

Many other doctors have been involved in the assesment and follow up of patients entered into the monotherapy trials. These include Drs S. Brown, D. Chadwick, P. Chesterman, C. Dellaportas, A. Heller, M. McGowan, B. MaCardle and S. Shorvon. Dr Shorvon gave me generous access to the initial analyses udertaken on the pilot trials and I gratefully acknowledge his subsequent interest and most valuable advice.

It is a particular pleasure to thank Dr A. L. Johnson for the considerable time he devoted to the development of appropriate methods of statistical analysis of seizure control. I was most fortunate not only to have his excellant guidance but also to work with a statistician

who understands the medical aspects of epilepsy and appreciates the necessary constraints of clinical practice. I am also indebted to Dr B. Ashworth for reading the text and his most usefull comments and cticisms.

Finally my wife Ruth has been of immeasurable help with the planning and preparation of the manuscript. She has been a constant source of support and encouragement and all my thanks go to her for the tolerance she has shown during the writing of this thesis.

ABSTRACT

Most studies of prognosis in epilepsy have been undertaken in patients with chronic seizure disorders. In contrast the patterns of seizure recurrence at the onset of the illness and the prognosis during the early years of treatment has received only scant attention in the literature. Three aspects of the early prognosis of epilepsy have been studied.

1). The prognosis for seizure control has been assessed in 106 patients with newly diagnosed previously untreated epilepsy who were followed prospectively for a median of 66 months. Patients were treated with phenytoin or carbamazepine monotherapy with extensive use of anticonvulsant level monitoring. Twenty six patients remained completely seizure free. Actuarial analysis showed that 35% of patients entered a seizure free period of at least two years at the start of treatment, 73% by four years and 82% by the end of 8 years. Once a remission had occurred relapses were usually isolated events, often related to poor compliance. The presence of partial seizures, a high pretreatment tonic clonic seizure frequency, a positive family history of epilepsy and the presence of symptomatic epilepsy and associated neurological, social and psychiatric handicaps predicted a

worse prognosis. In patients who continued to have seizures during the first two years of treatment the probability of subsequently achieving a remission had fallen by one half.

2). The prognosis for seizure recurrence was assessed in a series of 146 adults and children who presented within a median of one day following a first ever tonic clonic seizure. The cumulative probability of seizure recurrence was 60% by 1 year, 69% by 2 years and 71% by 4 years. Patients with symptomatic seizures and those who were aged under 16 had a higher recurrence rate.

3). The intervals between seizures were measured in a further series of 183 adults and children with two or more untreated tonic clonic seizures. The second seizure followed the first within a month in 30% and by one year in 87%. In patients with multiple untreated seizures the interval between consecutive seizures appeared to decrease with each seizure that occurred. The subsequent prognosis on treatment deteriorated as the interval between the first and second seizures shortened.

Following a first seizure the majority of patients are likely to develop epilepsy. The second seizure usually follows the first in rapid sucession and the early patterns of seizure recurrence are important in determining the

subsequent prognosis. After starting treatment as many as 80% of patients rapidly enter a prolonged period of seizure control, which in a substantial proportion of cases may be permanant. The early years of treatment are of crucial importance in determining the long term prognosis in epilepsy. Three quarters of all one year remissions began during the first year of treatment and the longer seizures continued the harder they were to treat. Further studies are needed to assess whether early or more effective treatment at the onset of the illness might improve the subsequent prognosis and reduce the proportion of cases who develop chronic epilepsy.

C O N T E N T S

CHAPTER ONE

LITERATURE REVIEW

A. INTRODUCTION

Amongst the many neurological disorders that afflict man, it is difficult to overestimate the central importance of epilepsy. It is one of the commonest disorders of the nervous system, the prevalence rate for active epilepsy being of the order of 4 per 1000 of the population (Zielinsky, 1976). Assuming an incidence rate of 50 per 100,000 and a life expectancy of 50 years, over 3% of the population can be expected to develop epilepsy at some time during their life (Hauser & Kurland, 1975). This figure excludes an even higher number who have only a single seizure or only experience seizures in relation to an acute precipitating event such as fever or alcohol withdrawal.

Epilepsy is also important because of the diversity of the disorder in terms of its causes, clinical features and complications. In some patients it appears to arise spontaneously in a perfectly healthy individual. In other instances, seizures may be only a symptom of an underlying acute neurological or systemic disorder or may arise as a complication of a wide variety of central nervous system

diseases. In those patients in whom the disorder becomes chronic the occurrance of seizures may be only one aspect of a disabling disorder with associated neurological, social and pyschiatric handicaps. Because three-quarters of cases occur before the age of 20, epilepsy (or its treatment) may adversely affect growth and development. Patients with epilepsy appear to be particularly prone to psychological complications; cognitive impairment, affective disorders and psychosis can all complicate the course of epilepsy. A diagnosis of epilepsy still carries with it a number of social implications, such as those affecting driving and employment. Furthermore, by its very nature, it often remains a hidden illness and the social stigma which is attached to it unfortunately still plays a part in the disease.

In this chapter a review of the literature relating to the prognosis of patients with epilepsy will be presented. A true understanding of the prognosis of epilepsy is of crucial importance. It affects not only our understanding of the nature of epilepsy but many diverse aspects of patient managment and clinical practice ranging from the appropriate counselling of individual patients and the development of rational treatment strategems, to the design and analysis of anticonvulsant trials. Once a diagnosis has been established, many questions and worries that understandably arise relate directly to the prognosis

of the disorder. What is the likelihood that seizures will be controlled? For how long will treatment be needed and can epilepsy be cured? Because the patient is often a young adult worries concerning driving, employment and child bearing are particularly common. The illness is still surrounded by much myth and misunderstanding. For many people the diagnosis carries with it the implication of a lifelong intractable disorder associated with mental deterioration. Unfortunately, in attempting to find an answer to these questions the physician will find little help from the currently available literature on prognosis. Much of it is highly contradictory in nature and virtually all of it has been based on the observation of a small sub group of patients with long standing chronic epilepsy. The gloomier views on prognosis, often to be found in the established textbooks, do not necessarily apply to the generality of patients.

A knowledge of the natural history and prognosis of epilepsy has a major bearing on two important treatment decisions, both of which arise commonly in clinical practice. Most neurologists in this country, recomend treatment after the occurrence of two or more seizures, particularly if they occur within the space of one year (Reynolds, 1987). A reasoned basis for this policy, however, cannot be found anywhere in the literature and the appropriate management is highly controversial

(Hauser, 1986; Elwes & Reynolds, 1988). The decision is of importance because once started treatment is usually given continuously for a period of many years. Although the majority of patients (if treated appropropriately) experience minimal toxicity it is only in comparitively recent years that the chronic side effects of anti-convulsants have become more widely appreciated (Reynolds, 1975). A broader qustion that will be considered in some detail later is whether the timing of initiation of treatment in any way affects long term prognosis. If this is indeed the case then it would have major implications on the way in which patients are managed. Similar uncertainties surround the decision as to when anticonvulsants should be discontinued (Chadwick, 1985). This important area has received even less attention in the published literature. It is only in comparatively recent years that the adverse factors associated with relapse following drug withdrawal have been more clearly delineated. The crucial questions as to how long treatment should be given to patients who are in remission and rate at which drugs should be withdrawn remain unanswered.

A knowledge of the prognosis of epilepsy also has a direct bearing upon other aspects of the rational treatment of epilepsy. Effective drugs have now been available for over a century. There is, however, remarkably little guidance

in the literature concerning the comparative efficacy and toxicity of the established anticonvulsant drugs. The single most important reason for this has been the poor design of anticonvulsant trials (Coatsworth, 1971). Most importantly, virtually all of these have been undertaken in patients with long standing intractable epilepsy where the prognosis is extremely poor. It is unlikely that meaningful results will be obtained by comparing efficacy in groups of patients who essentially are drug resistant. It is only in very recent years that trials have for the first time been undertaken using monotherapy in newly diagnosed patients. It is also important to appreciate the limits of currently available treatment. In patients in whom the chances of remission are low the physician is under pressure to try the addition of more and more drugs in an attempt to control what is, in fact, an intractable disorder. Unfortunately, this tendency has accelerated in recent years with the increasing number of new and experimental drugs which are available. Although the disadvantages of polytherapy are manifest, there is remarkably little evidence that the use of multiple drugs has any beneficial effect on the long term prognosis for seizure control (Reynolds & Shorvon, 1981).

Before considering the literature on the prognosis of patients with epilepsy a number of general observations should be emphasised. The prognosis of epilepsy has

always been a subject of considerable controversy. In one of the important 19th century texts, Reynolds (1861) opens the chapter on the prognosis of epilepsy by quoting the diametrically opposed views of two leading authorities:

> "J'en ai gueri un tres grand nombre".
> (Tissot, 1770)
> "Elle conduit presque unfailliblement a
> l'incurabilite par de lentes degradations".
> (Delasiauve, 1854)

The controversy has not abated with the passage of time. Rodin (1968), in probably one of the most influential and widely quoted works on the prognosis of epilepsy, concluded that the disorder was likely to be chronic in as many as 80% of patients. Although these views have been influential they have not gone unchallenged. In a more recent study, Annegers et al. (1979) concluded almost exactly the reverse, namely, that nearly three quarters of patients enter prolonged and usually permanent remission. Between these two extremes every shade of opinion is to be found. In patients presenting with single seizures the recurrence rate has been reported to vary between 29% and 69% and similar uncertainty surrounds the reccurrence rate following anticonvulsant withdrawal (Chadwick & Reynolds, 1985).

There are probably two main reasons for this disagreement. Firstly the outcome in epilepsy is indeed highly variable.

Some patients appear to experience only one or a few seizures occurring over a short period of time. Following effective treatment prolonged and sometimes permanent remissions occurs. In others the disease progresses, for reasons that are unknown, into a lifelong intractable disorder. Because of the inherent variability of outcome the methods of patient selection are of fundamental importance in determining the results of prognostic studies. If these are not clearly stated (and unfortunately this is the case in a very large number of reports) then interpretation of the results is rendered virtually impossible. A similar consideration underlies the widely varying reports of recurrence rates following a first seizure. It will be argued at some length in the experimental sections and the subsequent discussions that this has been the single most important factor determining the controversy surrounding the prognosis of epilepsy.

A second difficulty in interpreting the literature is the heterogenicity of epilepsy. There is even difficulty in reaching a satisfactory definition of the disorder. Some authors include patients with acute symptomatic seizures (Blom et al. 1978; Goodridge & Shorvon, 1983; Hirtz et al. 1984) whilst other authors include those with a single attack and an abnormal EEG (Okuma & Kumashiro, 1981). Under the broad heading of epilepsy it is possible to identify groups of patients in whom the prognosis is known

to differ widely. Although Rolandic seizures may appear identical to focal motor attacks arising secondarily to structural disease of the cortex, the natural history may be very dissimilar (Lerman, 1985). Childhood absence seizures may be difficult to distinguish from seizures arising from discharges in the temporal lobe. In the former, there is a striking tendency for the disease to undergo spontaneous remission (Aidie, 1924) whilst the latter is one of the commonest seizure types amongst patients with chronic intractable epilepsy. In recent years the International League Against Epilepsy has put forward proposals for the classification of epileptic seizures and also of the epilepsies and epileptic syndromes (Commision on Classification & Terminology 1981 & 1985). The authors rightly admit that the classificat-ions are likely to be temporary and should be considered a basis for further discussion. Despite this, they are an important summary of our current knowledge. In the first part of this chapter the historical and theoretical basis for the proposed classification will be briefly reviewed. The importance of this will subsequently become apparent as it appears that many of the proposed subdivisions have important prognostic implications. Furthermore in many of the proposed epileptic syndromes the prognosis is pivotal in establishing its nosological position.

It is impossible to consider the prognosis of epilepsy in isolation from its treatment. Although methods such as diet or surgery have an important role in small selected groups, the use of drugs has always been, and still remains, the mainstay of treatment. There is now overwhelming evidence that the currently available drugs are highly effective in suppressing seizures. A central part of this thesis is an attempt to assess the impact that these drugs have had on the prognosis of patients with epilepsy. Do they merely suppress seizures, or in doing so do they actually alter the natural history of the disorder and bring about a cure? An answer to this question implies a knowledge of the natural history of untreated epilepsy. There is virtually no guidance in the literature on this and any attempt to explore this experimentally is limited by obvious ethical and practical considerations. If anticonvulsants do however alter the natural history of epilepsy then there are many important implications for the practical management of patients. A related question is whether there are significant differences in efficacy between the currently available drugs. Although modern compounds such as carbamazapine are probably less toxic, is there any evidence that they are any better in controlling seizures? The difficulties in establishing secular trends in prognosis will be examined, particularly as some more recent studies have attributed improvements in prognosis to advances in drug treatment

(see for example, Okuma & Kumashiro, 1981).

In the literature review considered here and the discussions to each of the chapters considerable emphasis has been placed upon the historical literature. There are a number of reasons for this. The second half of the Nineteenth Century was a time when a major expansion of knowledge about epilepsy took place. Patients, who had previously been incarcerated with the insane, benefited from the humanisation of treatment that occurred in the previous century (Temkin, 1971). Specialised institutions such as the National Hospital for Paralysed and Epileptic in London and similar hospitals in Europe and North America were established. These institutions provided, for the first time, the opportunity to observe large numbers of patients with the disorder. The physicians who staffed these hospitals, such as Hughlings Jackson, Delasiauve and Reynolds produced monographs and books specifically devoted to epilepsy. Their work has had a very major impact on our understanding of the disorder. Difficulties surrounding the diagnosis, classification, treatment and prognosis are described with a clarity and force by these authors which make them relevant to this day. The specific area of interest in this thesis is the early prognosis of epilepsy; the probability of seizure recurrence following a first seizure, the patterns of seizures at the onset and the early response to treatment.

It is curious that until very recent years these aspects of the natural history of epilepsy have received virtually no attention in the Twentieth Century literature. Indeed, the most detailed and complete account of this work is probably found in historical literature written over a hundred years ago by Gowers (1881). His work is of particular interest because he was able to observe the natural history of untreated epilepsy and subsequently document the major impact of the introduction of bromides. Gowers also stated that prior to the introduction of these drugs spontaneous remission was most unusual, thus implying that treatment did indeed alter the natural history of epilepsy. Gowers' observations on the ealy prognosis of epilepsy will be re-examined and their implications for further research discussed.

B. THE NATURE OF EPILEPSY: HISTORICAL LITERATURE

Throughout the ages the term epilepsy has been surrounded by superstition and myth. The word itself is derived from the Greek verb "epilambanen" meaning to seize or to attack. During an epileptic seizure the victim was thought to be seized by some demon or evil force. To this day a dignosis of epilepsy still carries with it a social stigma, and the concept that it is an unclean disease has lingered on.

1. The Sacred Disease.

The first historical account that we have of the disorder, which we now recognise as epilepsy, is to be found in the Hippocratic Writings dating from around 400 B.C. (Temkin, 1971). The book "On the Sacred Disease" was written by a physician but directed at a lay audience and was an attack on popular superstitions and the magicians and charletons who termed the disease "Sacred". According to the author epilepsy was no more sacred or divine than any other disease. It's causes lay within the brain and it was, therefore, open to treatment by physical means. During the second century A.D. the centres of knowledge moved to Alexandria and the teachings of Galen (130-200 AD) predominated. The cause of epilepsy was thought to be an

excess of moist humour or phlegm blocking the ventricles of the brain. The seizure was the outward manifestation of the body's attempt to rid itself of this blockage.

These teachings were of profound importance for the subsequent development of our understanding of epilepsy. They refuted the superstitious and demonical concept and formed the basis of the development of rational investigation that occurred during the enlightenment. Although the theory of humours may strike us as fanciful, the classification of the causes of epilepsy proposed by the Ancients form the basis of modern theories (see below).

2. The Falling Sickness

Temkin (1971) claims that during the Middle Ages little was added to our understanding of epilepsy. Other conditions losely described as states of possession, raptures or prophetic trances, or indeed any disorder which caused a sudden fall were included under the term "morphus caducus", or the "falling sickness" well known from Shakespeare's Julius Ceasar. Periodic states of mania and epilepsy were not clearly distinguished from each other and both were felt to be associated with phases of the moon, a concept which still persists in our use of the term lunacy. The horror and revulsion that

were felt by the ignorant who witnessed the unfortunate victim during a seizure were propagated by the conviction that epilepsy was a contagious disease. People would spit upon the epileptic and refuse to eat or drink with him. Epilepsy was classed along with the great contagious diseases, leprosy, the plague and subsequently syphilis.

In the Gospel of St. Mark, Chapter 9, 14-29 Jesus casts out an unclean spirit from an epileptic child who is cured of the disorder. Throughout the Middle Ages the Church tried to dispel the pagan beliefs of witchcraft and lunacy. Certain saints, particularly St John the Baptist and St. Valentine, became associated with epilepsy. In the Fifteenth Century a hospital for epilepsy was built at the Priory of St. Valentine in Rufuch, Alsace. The medieval physicians accepted the force of evil without question and a great debate arose as to the relationship of epilepsy to possession, witchcraft and magic.

3. Idiopathic Epilepsy

The relationship of epilepsy to structural disease of the brain has always been a subject of controversy. These difficulties are well illustrated by tracing the historical development of the term "idiopathic or "essential " epilepsy. The origins of the debate lie in the teachings of Hippocrates and Galen. The ancients

recognised that epilepsy was a disease of the brain. In true or idiopathic epilepsy the sustance of the brain was normal and the seizures were caused by an obstruction of viscous humours within the ventricles. However, it was also recognised that seizures could arise from structures outside of the brain. An "aura" or breeze could arise from other organs, particularly the heart, and spread to the brain causing a seizure. This type of epilepsy was termed sympathetic.

With increasing knowledge, particularly of pathological anatomy that occurred during the Renaissance, this classification was modified. It became apparent that in the great majority of cases of epilepsy, the post mortem examination of the brain appeared normal. In the words of Esquirol: ".... Let us admit frankly that up to now pathological anatomy has shed little light on the immediate seat of epilepsy". (Esquirol, 1838; quoted by Temkin, 1971, page 273).

On the other hand, by the Eighteenth Century it was known that fractures of the skull, softening or haemorrhage into the brain or syphylitic gummas could all cause seizures, indistinguishable from those that occurred in epilepsy (Penfield & Erikson, 1941). Furthermore, it was subsequently appreciated that eclamptic convulsions could occur in the context of other diseases. Most important of

these were infantile eclampsia, puerperal eclampsia and eclampsia that followed uraemia or Bright's disease (Gowers, 1881). The ancient classification of epilepsy was modified to take account of this new knowledge. Thus Delasiauve suggested the following:

1. "Essential or idiopathic epilepsy, manifesting itself merely in functioning deviations, without lesion, corresponding to simple nervous afflictions and, in a word, constituting a veritable neurosis.
2. Symptomatic epilepsy belonging to a more or less appreciable cerebral lesion, the convulsive spasm being here the symptom and not the disease.
3. Finally, a third epilepsy, called sympathetic, produced by the radiation of abnormal impressions which can have their seat in all parts of the body except the brain or its appendages".

(Delasiauve, 1854; quoted by Temkin,1971, page 289)

Controversy continued to surround what constituted true or essential epilepsy. Sieveking (1858) stated that it was impossible to distinguish between essential and nonessential, idiopathic and symptomatic epilepsy and the classification should therefore be abandoned (quoted by Temkin, 1971). On the other hand, Reynolds (1861) considered only idiopathic epilepsy to be the true disorder.

> "In this volume I propose treating only of epilepsy proper, viz. of that form of idiopathic convulsions of which I believe alone the name epilepsy must be applied.... We must employ the term epilepsy in a restrictive sense implying only those cases which, in the present state of medical science, are irreducible".
>
> (Reynolds, 1861)

Hughlings Jackson chose to study seizures arising from well defined lesions of the cerebral cortex. In his later work (Hughlings Jackson, 1873) he went on to conclude that all seizures, whether focal or generalised, must have a structural basis if only sufficient means were available to detect them. In this sense he denied the existence of idiopathic epilepsy (see Temkin, 1971 page 349 et seq.). Gowers, who was Hughlings Jackson junior colleague, accepted his teaching that seizures were caused by excessive discharges of grey matter. However he classified epilepsy as a functional disorder of the brain with disorders such as hysteria and chorea. Although Gowers admitted that seizures could arise in the presence of a gross lesion within the substance of the brain epilepsy was, in his own words, "a disease of tissue not of structure" (Gowers, 1881).

4. Epilepsy and Cerebral Localization

Our present understanding of the importance of cerebral localization in causing the symptoms of epileptic seizures originates from the work of Hughlings Jackson (Penfield & Erickson, 1941). Prior to his most important papers, published between 1850 and 1870 it was considered that in true or essential epilepsy convulsive movements occurred on both sides of the body and consciousness was lost

(Reynolds, 1861). Hughlings Jackson, however, chose to study unilateral convulsions which have, of course, been eponymously named after him. In deference to the current theories, he termed these attacks "epileptiform" to distinguish them from true seizures, although he subsequently made it clear that he considered that the underlying mechanism in both were in fact the same (Hughlings Jackson, 1873).

Hughlings Jackson attributed the first description of unilateral seizures to Bravais in 1827. Bright, between 1831 and 1835 described unilateral seizures in which consciouness was preserved, and furthermore that these episodes could be associated with gross lesions affecting the cerebral cortex opposite to the side that convulsed. Most important of Hughlings Jackson's forerunners were the Swiss Neurologist Herpin to whom he made many references. Herpin based his analysis on 300 cases seen in a private clinic (see Temkin, 1971 pages 324 et seq). He found that in over half the cases minor attacks, cramps, spasms or vertigos preceded the occurrence of major seizures. Variable as these might be, they were remarkably constant in any given patient. Herpin proposed that these were in fact incomplete or abortive attacks. The aura was not a sensation that started peripherally and spread to the brain causing a seizure, but the start of the seizure itself.

Hughlings Jackson's work was based upon a combination of meticulous medical observation and pathological examination. Broca had already proposed in 1861 that speech was associated with left hemisphere function. Hughlings Jackson found that unilateral motor seizures were usually associated with lesions of the opposite precentral gyrus. Similarly, in dreamy states a lesion was often found within the temporal lobe (Hughlings Jackson & Colman, 1898). Thus the symptoms of the attack depended upon the area of the brain which was affected. If there was a destructive lesion of the brain then paralysis would occur. A seizure was a reverse of this process and the movements were due to the excitability of the nervous elements. According to Hughlings Jackson, seizures were due to "occasional, sudden, excessive, rapid and local discharges of grey matter" (Hughlings Jackson, 1873). A tumour, infarction or some other gross lesion of the brain was necessary in order to cause the excessive discharges and because of the episodic nature of the symptoms, some other form of irritation or reflex action was needed to bring about the seizure. In 1870 Fritz and Hitzig described the electrical excitability of the cerebral cortex in dogs. They observed that electrical stimulation of the precentral gyrus could cause muscular contractions and that more prolonged stimuli produced convulsions. This in association

with the work of Ferrier provided experimental evidence to support Hughlings Jackson's theories and heralded the modern era of the study of epilepsy.

C. The Classification of Epilepsy

Although the occurrence of seizures is common to all types of epilepsy, the individual features of the disorder may differ greatly. Any attempt to classify epilepsy must take account not only of seizure type, but also EEG features, age of onset, associated clinical features, presumed etiology and the response to treatment and prognosis. In the current state of knowledge it is not possible to classify epilepsy on the basis of disease states. The term "disease" implies a known pathophysiology or morbid pathology, a uniform set of clinical symptoms and signs and a predictable outcome. As yet few diseases, such as might be said to occur in Lafora body disease or Unverricht-Lundborg disease, have been identified (Berkovic & Andermann, 1986). It is, however, possible to group together patients on the basis of a particular feature or group of features that occur sufficiently frequently to constitute a syndrome. A syndrome does not necessarily imply a single aetiology and the symptoms of one syndrome may overlap with another.

In recent years the Commission on Classification and Terminology of the International League against Epilepsy (1981 & 1985) has attempted to summarise the current knowledge and produce a broadly acceptable classification. Because of the diversity of terminology found in the

literature there is general agreement that a uniform method of classification is needed to allow comparison of results and to aid communication. The league initially proposed a classification of epileptic seizures (in its original and revised forms) which has now become widely accepted and more recently a classification of the epilepsies and epileptic syndromes.

A summary of the proposed classification is shown in Table 1:1. It should be noted that a number of disorders are excluded from the broader definition of epilepsy and have been placed under a separate heading in Section 4. These include patients with seizures occurring in the context of systemic precipitating factors such as fever, isolated seizures and epilepsy characterised by specific modes of precipitation, e.g. musicogenic epilepsy. The division of the remaining epilepsies is made along the grounds considered in the previous historical section, the principle one being into partial (or focal) and generalised epilepsies.

1. Partial and Generalised Epilepsies

Partial epilepsies are defined as those in which the symptoms of the seizure or the investigative procedures such as EEG or neuroimaging show a localised origin for the attacks. The focus may be either anatomical or functional.

TABLE 1:1. THE CLASSIFICATION OF THE EPILEPSIES AND EPILEPTIC SYNDROMES (Adapted from Commision on Classification and Terminology, 1985)

1 PARTIAL EPILEPSIES

A) IDIOPATHIC
Benign Epilepsy of Childhood with Centro-temporal Spikes
Childhood Epilepsy with Occipital Paroxysyms

B) SYMPTOMATIC

Frontal Lobe	Motor Cortex
Supplementary Motor	Temporal Lobe
Cingulate	Parietal Lobe
Anterior Frontal	Occipital Lobe
Orbito Frontal	Dorsolateral

2 GENERALISED EPILEPSIES

A) IDIOPATHIC
Benign Neonatal Familial Convulsions
Benign Neonatal Convulsions
Benign Myoclonic Epilepsy in Infancy
Childhood Absence Epilepsy
Juvenile Myoclonic Epilepsy
Epilepsy with Grand Mal Seizures on Awakening

B) IDIOPATHIC or SYMPTOMATIC
West Syndrome
Lennox-Gastaut Syndrome
Epilepsy with Myoclonic-astatic seizures
Epilepsy with Myoclonic Abscences

C) SYMPTOMATIC
Malformations,eg. Sturge Weber Syndrome
IEOM eg. Phenyl Ketonuria
Storage Diseases eg. Tay Sachs, Cereboid Lipofuscinosis

3 UNDETERMINED PARTIAL or GENERALISED EPILEPSIES
Neonatal Seizures
Epilepsy with Continuous Spike Waves during Slow Wave Sleep
Acquired Epileptic Aphasia

4 SPECIAL EPILEPTIC SNDROMES
Febrile Seizures
Acute Symptomatic Seizures
Isolated Seizures
Specific Precipitants, eg musicogenic epilepsy
Chronic Progressive Epilepsia Partialis Continua of Childhood

It is also recognised that the focus may be poorly defined, multiply or occur in different hemispheres as in the benign partial epilepsies of childhood (Lerman & Kivity, 1986).

The partial epilepsies are divided into different groups pepending on the area that is involved in the ictal discharge. These groups have been ascertained not only on the basis of clinical observation and EEG and video monitoring but also in some cases from the use of depth electrodes. In addition to the more widely recognised temporal lobe epilepsies, descriptions of 9 other partial epilepsies are given in the classification.

Generalised epilepsies are those in which the first clinical changes of the seizure indicate involvement of both hemispheres. The ictal encephalographic pattern is initially bilateral. It is accepted that there are patients in whom it is not possible to determine whether the epilepsy is partial or generalised and these are placed in a separate section, no.3 in Table 1:1. These include patients in whom both focal and generalised seizures do indeed appear to occur together and those in whom the EEG and clinical features do not permit classification.

2. Idiopathic and Symptomatic Epilepsies

The partial and generalised epilepsies are further subdivided into idiopathic and symptomatic forms. It is rightly proposed that the terms primary and secondary should not be used as these cause confusion, primary and secondary generalised being more correctly a description of seizure type. The authors admit that this distinction can give rise to difficulties and that in many cases there appears to be an interaction of causative factors such as an hereditary disposition, structural brain disease or acute exogenous factors.

3. Epileptic Syndromes of Childhood and Adolescence

An important aspect of the international classification is the proposal of a number of specific epileptic syndromes. It is striking that all of these are confined to childhood or adolescence and indeed the classification places much emphasis on age related onset. The syndromes are shown in Table 1:2 where they have been arranged in chronological order of maximum age of onset. Although there is some overlap they may be conveniently divided into four main groups: neonatal seizures, seizures occurring in infancy and childhood, childhood seizures and finally those occurring in adolescence (Roger et al, 1985). Neonatal seizures constitute a specialised group and will not be

TABLE 1:2 EPILEPTIC SYNDROMES OF CHILDHOOD AND ADOLESCENCE ARRANGED BY AGE of ONSET.

	AGE OF ONSET *	
	Maximum	Range
A) NEONATAL		
Benign Neonatal Convulsions		
Benign Neonatal Familial Convulsions	within 28 days	
Early Myoclonic Epilepsy		
B) INFANCY AND CHILDHOOD		
West Syndrome	5 months	0-1 year
Severe Myoclonic Epilepsy in Infants	6 months	0-1 year
Benign Myoclonic Epilepsy in Infants	NS	6 months-3 years
Myoclonic Astatic Epilepsy	3 years	0-8 years
Lennox-Gastaut Syndrome	4	1-10 years
C) CHILDHOOD		
Landau-Kleffner Syndrome	4 years	2-11 years
Epilepsy with Continuous Spike Waves during Slow Wave Sleep	4 years	8 months-11 years
Childhood Abscence Epilepsy	6 years	3-13 years
Benign Childhood Epilepsy with Centro-temporal Spikes	9 years	3-13 years
D) CHILDHOOD AND ADOLESCENCE		
Juvenile Abscence Epilepsy	13 years	10-17 years
Juvenile Myoclonic Epilepsy	15 years	8-26 years
Epilepsy with Grand Mal on Wakening	15 years	6-24 years

* From Roger et al, 1985.

considered in detail here. Some of the syndromes are extremely rare, such as epilepsy with continuous spikes and waves during slow sleep (Tassinari et al, 1985) and acquired epileptic aphasia (Beaumanoir, 1985(a)). Others, particularly the syndrome of epilepsy with grand mal seizures on awakening (Wolf, 1985) contain a very broad group of patients and the nosological position remains unclear. Five of the syndromes are different forms of myoclonic epilepsy, yet according to Gastaut et al (1975), these account for no more than 4% of cases in children (after exclusion of the Lennox-Gastaut Syndrome) and a similar proportion in adults.

Amongst the remaining epileptic syndromes there are four that are of particular importance and the important clinical features will be briefly presented here. West Syndrome, consists of the triad of infantile spasms, psychomotor retardation and the characteristic EEG finding of hypsarrthmia (Gibbs & Gibbs, 1952). In the idiopathic form, which occurs in one third of cases, there is normal psychomotor development up to the time of onset of seizures (Bellman, 1983). In the remaining cases it arises from a wide variety of central nervous system disorders including pre and perinatal damage, neurocutaneous syndromes (especially tuberose sclerosis), cerebral malformations, metabolic disorders and cerebral infections (Jeavons 1986). Mental retardation always occurs and is usually severe.

The term "petit mal" was introduced by Esquirol in 1815 to include all nonconvulsive epileptic seizures and was used in this manner by other 19th Century authors such as Gowers and Reynolds. The first description of what is now called childhood absence epilepsy, was given by Tissot.

> "In the intervals between major attacks, the young female patient had frequently had very short minor attacks which were recognised only by an instaneous loss on consciousness which stopped the patient's speech, accompanied by a very slight movement in the eyes. Often, on recovery, she completed the sentence which was interrupted; on other occasions she had totally forgotten it".
> (Tissot, 1770; quoted by Loiseau, 1985)

By the end of the Nineteenth Century petit mal was recognised as a specific form of epilepsy in the German literature and the term Friedman's disease was introduced. The most striking feature of the disorder, characterised by the large number of attacks which occurred, led to the use of the term "pynknolepsy" derived from the Greek "pyknos" meaning crowded or frequent (Sauer, 1916). In 1937 Gibbs, Gibbs and Lennox described the three per second spike and wave abnormality on the EEG that we now recognise as an integral part of the syndrome.

Although this was a major advance in our understanding it was subsequently proposed that the term "petit mal" should be applied to all cases in which this abnormality was seen,

regardless of the clinical picture. It became apparent that other seizure types, particularly myoclonic and atonic seizures, could occur as well as absence attacks and the term "petit mal triad" was introduced (Lennox, 1945). Matters were complicated further when it was shown that slow or atypical spike and wave could be associated with a type of epilepsy that had a worse prognosis and a high instance of associated neurological handicap, so called petit mal variant (Lennox & Davies, 1950).

The clinical features of petit mal variant were more fully described by Gastaut and colleauges and is now widely known as Lennox-Gastaut syndrome (Gastaut, 1982). The most important feature of the syndrome appears to be the seizure types. These take the form of tonic seizures, atypical abscences and myoclonic or atonic attacks (Beaumanoir, 1985(b)). The seizures occur many times a day, falls and injuries are particularly common and status epilepticus occurs in as many as two thirds of patients. One third of cases occur in otherwise healthy children and the remaining have mental retardation or neurological deficits arising from diverse aetiologies. In addition to showing the characteristic slow spike and wave the background rhythms are also slowed. The condition is usually resistant to treatment with currently available drugs.

In comparitively recent years a number of epileptic syndromes collectively known as the "benign partial epilepsies of childhood" have been identified. These are characterised by striking focal EEG abnormalities in the absence of strucutural brain disease, a strong familial tendency and a good prognosis. Benign partial epilepsy with centro-temporal spikes (Rolandic Epilepsy) appears to be the commonest and has received most attention (Lerman & Kivity, 1986).

As in Lennox-Gastaut syndrome the EEG features were defined before the characteristic clinical presentation was identified. Gibbs & Gibbs (1959-1960) identified 739 patients who had mid-temporal spikes on their EEG. In contrast to those with anterior temporal spikes, who tended to have psycho-motor seizures and a poorer prognosis, it was found that the EEG abnomalities in these patients rarely persisted beyond the age of 15 years. A number of studies have subsequently shown that mid-temporal spiking on the EEG can occur in apparently normal subjects with no evidence of clinical seizure disorders (Smith & Kellaway, 1964; Eeg-Olofsson et al, 1971; Cavazutti et al, 1980; Lerham and Kivity, 1981).

The initial clinical description of the disorder has been attributed to Nayra & Beaussart (1958). Important series have subsequently been published by Lombroso (1967) and

Lerhman & Kivity (1975). Three-quarters of cases occur between the ages of 5 and 10 years; it is most unusual for the onset to occur before the age of 3 or after the age of 15. The seizures often take the form of unilateral parasthesiae around the mouth and twitching of the face, lips and tongue. These attacks occur in complete clarity of consciousness and are accompanied by speech arrest and drooling of saliva. The seizures may become secondarily generalised, especially during sleep and many cases may be initially diagnosed as noctural grand mal epilepsy unless the characteristic EEG features are identified. Although the great majority of patients appear to have no associated neurological abnormality this does not exclude the diagnosis. Blom et al (1972) described 3 patients with rolandic epilepsy who had a hemiparesis. Three patients in the series of Lerhman and Kivity (1975) had cerebral palsy. In as many as 40% of cases a family history of a seizure disorder is obtained (Lerhman, 1985).

Epidemiological surveys of childhood epilepsies which have used EEG criteria in classifying the seizure types have suggested that rolandic epilepsy is not uncommon. Cavazutti (1980) in a retrospective survey identified 178 children between the ages of 5 and 14 who had experienced two or more afebrile seizures. Twenty-four per cent had rolandic epilepsy and 42% suffered other forms of partial epilepsy. Heijbel et al (1975) identified 70 new cases of newly

diagnosed seizure disorders in children between the ages of 1 and 15. Rolandic epilepsy was diagnosed on the basis of EEG features alone. In 16% focal discharges occurred in the rolandic area and an identical percentage had other forms of partial epilepsy.

Other forms of benign partial epilepsy of childhood have been proposed. Gastaut (1985) has described 63 cases of "benign epilepsy of childhood with occipital paroxysms". The age of onset ranged from between 15 months to 17 years of age. The great majority did not have evidence of structural brain disease and a family history of epilepsy was available in as many as one third of cases. Visual ictal symptoms consisted of either formed or nonformed halucinations and nearly one half had other seizure types. The striking diagnostic feature was prominent occipital spiking on the EEG that was very responsive to eye opening. According to Gastaut a significant proportion of patients develop hemicrania, nausea and vomiting whilst others develop complex partial seizures. Complete seizure control was achieved in 60% of cases. Benign partial epilepsy with affective symptoms (Dalla Bernardina et al, 1985) and with extreme somato-sensory evoked potentials (Tassinari & De Marco, 1985) have been described. The term has been expanded by Dalla Bernardina et al (1985) to include all partial epilepsies occurring in childhood in which there is no evidence of structural brain disease.

D. THE TREATMENT OF EPILEPSY

1. Historical Literature

The remedies that have been used for the treatment of epilepsy throughout the ages are legion. Each new theory as to the nature or causes of epilepsy has led to novel therapeutic endeavours. Temkin (1971), in his authorative review of the historical literature, gives an extensive account of the different treatments that have been used. Reynolds (1861), writing before the introduction of bromides, said this of the treatment of epilepsy.

> "Perhaps no disease has been treated with more perfect empiricism on the one hand, or more rigid rationalism on the other, than has epilepsy. Unfortunately, both methods have often completely failed; the former as it must do in a proportion of cases; the latter in still larger numbers, because the theories upon which it has rested have often been abundantly wrong"
>
> (Reynolds, 1861)

Although many of the treatments that have been used were based on superstition, myth or theories that would now strike us as bizarre, they are of importance because they reflect the changing understanding of the nature of epilepsy.

Many of the treatments for epilepsy, which continued to be used even until the middle of the Nineteenth Century, can

be traced back to the ancient theories of Hippocrates and Galen. As idiopathic epilepsy was caused by a collection of moist phlegmatic humours within the ventricles of the brain, treatments were directed at relieving this obstruction. It was important that the correct food should be eaten; dry bread and herbs which were acrid and cleansing were prescribed, whilst moist substances such as cucumber and melon were forbidden. Cauterization of the scalp was performed prophylacticaly on children in the Middle Ages to prevent the development of epilepsy. Similarly purges, blood letting or application of leaches to the scalp were all used to avoid the accumulation of humours.

Epilepsy arising from other organs, so called sympathetic epilepsy, needed different remedies. If a seizure started in a limb then a ligature should be placed upon it or some strong medicine such as mustard applied. Despite the teachings of Hughlings Jackson, Gowers also advocated this form of treatment. An extension of this concept led to barberous practices. Following the reflex theories of Hall and Brown Sequard, amputation of the limb, castration or even tracheostomy to relieve respiratory obstruction was carried out.

The use of drugs have always played a central part in the treatment of epilepsy. According to Temkin the use

of herbs, drugs or specifics were often particularly associated with superstition and the occult. He quotes the Greek physician Dioscurides who listed forty five substances for the treatment of epilepsy. At least thirteen of these had superstitious origins such as hare's rennet, amulet of stones found in the stomach of swallows, storks dung and other such remedies. Reynolds (1861) quotes the following example of a specific remedy:

> "Take the powder of Osmond, and the root of peony and the powder of Moztegan, and drinke all these with stale ale and let them say their prayers; and as soon as the Party falleth downe and give the sicke to drinke with good ale that is stale, and by God's grace he shall never have the falling evil any more: proved."
> (Leuens P. 1632)

With the enlightenment such remedies fell into disuse although Reynolds himself was impressed by results of mistletoe in the treatment of epilepsy and recommended a new trial. The texts of the Nineteenth Century contain lists of drugs that had been tried in the treatment of epilepsy, with varying claims of success (Shorvon, 1987).

As the superstitious remedies of an earlier age were discarded, others of an equally dubious nature were introduced. Drugs such as strychnine were overtly dangerous whilst salts of silver were extremely toxic and caused an unpleasant discolouration of the skin. Many of the drugs

such as chloroform, opium, belladonna, cannabis, selenium (marsh parsley) and cotyledon umbilicus (pennywort) were sedatives, and this was thought to be their mode of action in the treatment of epilepsy (Friedlander, 1986). It was in this context that probably the single most important advance in the treatment of epilepsy occurred.

2. The Introduction of Bromides

Bromides were included in the British Pharmacopia of the first half of the Nineteen Century for the treatment of splenomegaly. Their introduction for the treatment of epilepsy has been attributed to a remark made by Sir Charles Lowcock. At a meeting of the Royal Medical and Chirurgical Society in 1857, Sieveking presented an analysis of 52 cases of epilepsy. Lowcock, who was president of the society commented in the discussion (Sieveking, 1857) that dentition and onanism were frequent causes of epilepsy. He went on to say that epilepsy associated with the menstrual cycle was particularly difficult to treat and that he had previously read of some work by a German doctor who had claimed that bromide of potassium produced temporary impotence and loss of virility. He (Dr. Lowcock) had therefore tried the drug in fifteen cases of epilepsy in women associated with hysteria and found that it had cured fourteen of them.

Despite the rather dubious theoretical basis potassium of bromide became widely used in the treatment of epilepsy. The identity of the German doctor has never been established and Lowcock has been credited with their introduction although his contribution was small (Joynt, 1974). Four years later Wilks (1861) stated that he used the drug in all new cases of epilepsy and that it was "singularly efficacious". Gowers in 1881 wrote this of it:

> "The indications of the prognosis have been materially changed by the introduction of Bromides. Not only do they arrest fits far more frequently than any other remedy, but they are effective in cases which, according to experience previous to the introduction of these remedies, would have been regarded as most unpromising."
>
> (Gowers, 1881)

According to Gordon Holmes, by the end of the Nineteenth Century, 2.5 tons of the drug were used every year by the National Hopsital, Queens Square (quoted by Temkin, 1971 page 299).

More recent testament as to their efficacy is available. Pollock (1938) claimed that 61 out of 85 cases (72%) had a remission of one year or more after treatment with sodium bromide. Of particular interest is the paper by Arieff (1951) in which he summarised his experience over a twelve year period. It was his practice to start treatment initially either with bromide or phenobarbitone given

alone, and if these failed, phenytoin was substituted or added. Out of 118 cases who were given sodium bromide seizures were completely controlled in 83% for periods ranging from six months to two years or longer. Similar remissions (80%) were obtained in 91 cases given phenobarbitone. The use of phenytoin in those cases which failed on treatment did little to improve the prognosis. Livingston (1958) claimed the drugs were particularly efficacious in childhood epilepsy asociated with organic brain disease, and that they were safe to use and free of serious side effects if serum levels were monitored (Livingston & Pearson, 1953).

3. Modern Anticonvulsant Drugs

It is probably correct to look upon bromides as the fore runner of modern anticonvulsant drugs. In the last century a whole series of drugs have been introduced which may be divided into eight main groups as shown in table 1:3. Some of them, such as phenturide, the different hydantoin derivatives, troxidone and sulthiame are not now widely used. It is beyond the scope of this review to consider all of these drugs in detail but there are a number of important principles that can be shown by briefly examining the development of the more important compounds.

Barbituric acid was first synthesized in 1863 and

TABLE 1:3 CONTEMPARY ANTICONVULSANT DRUGS, WITH DATE OF FIRST CLINICAL REPORT (Adapted from Shorvon,1987)

Acetylurea:	Phenturide, 1949
Barbiturates:	Phenobarbitone, 1912 Primidone, 1952
Benzodiazepines:	Nitrazepam, 1963 Diazepam, 1965 Clonazepam, 1976 Clobazam, 1980
Dipropylacetate:	Sodium Valproate, 1964
Hydantoins:	Phenytoin, 1938 Methoin, 1956 Albutoin, 1967
Iminostilbene:	Carbamazepine, 1962
Oxazolidinediones:	Trimethadione, 1945
Succinimides:	Phensuximide, 1951 Ethosuximide, 1958
Sulphonamides:	Acetazolamide, 1955 Sulthiame, 1960

phenobarbitone, a stable derivative, was developed in 1912. An extensive German literature confirmed its sedative actions and paradoxically it was for this very reason that it was introduced for the treatment of epilepsy (Hauptmann, 1912). During the first three decades of the Twentieth Century barbiturates replaced bromides in the treatment of epilepsy, largely because they were less toxic. The discovery of the anticonvulsant properties of phenytoin by Putman and Merritt was an important advance for two reasons. Firstly, the drug was tested in an experimental animal model prior to being given to human subjects. Secondly, on the basis of animal experimentation and clinical usage it became apparent that the sedative and anticonvulsant properties of the drug could be separated (Merritt et al, 1938; Merritt & Putnam, 1938).

According to Friedlander (1986), neither of these concepts was new. The ability of absinthe, picrotoxin and metrazole to cause seizures had already been established and used for evaluating anticonvulsant drugs. Furthermore, non-sedating treatments for epilepsy were available such as borotartrate, vital dyes and ketogenic diet. Merritt and Putman, however, have been credited with both these discoveries (Rowland, 1982) and the use of animal models for the testing and development of new drugs has subsequently become widespread.

Trimethadione was found to be effective in controlling seizures not only in electro-shock models of epilepsy (as was the case in phenytoin) but also in metrazole induced seizures and the first trial was undertaken by Perlstein (1945). Unlike bromides and phenytoin the drug was found to be particularly effective in the treatment of petit mal. Phensuximide (Zimmermann, 1952) and ethosuximide (Zimmermann, 1958) were subsequently introduced and the latter has remained an established drug for the treatment of petit mal, largely because it was less toxic than the previous therapies that were used in the treatment of absence seizures.

The introduction of benzodiazepines for the treatment of epilepsy bears a marked resemblance to the discovery of phenobarbitone. The drugs were introduced during the early 1960s and used for their sedative and anxiolytic effects and was subsequently found to have anticonvulsant properties (Brock and Dyken, 1963). Diazepam was shown to be effective in controlling status epilepticus in animals and was given intravenously to humans by Naquet et al (1965). The more modern 1-5 benzodiazepines such as clobazam are said to retain anticonvulsant properties but to be less sedative (Robertson, 1986).

Of more importance has been the development of carbamazepine and sodium valproate. The first of these was derived

from an antihistamine from which two important compounds were obtained, imiprimine and carbamazepine. On the basis of its chemical structure it was predicted to have anticonvulsant properties and the first trials were undertaken in the early 1960s (Lorge, 1963). Sodium valproate (diproprionylacetic acid) was synthesised in 1882 and used as an organic solvent for eighty years until its anticonvulsant properties were discovered accidentally in mice in 1963 and clinical trials were undertaken a year later (Carraz et al, 1964).

4. Unsatisfactory Aspects of the Drug Treatment of Epilepsy

There is now a wealth of clinical and experimental evidence, extending over a period of more than a century, to show that the drugs currently available for treating epilepsy are highly effective in suppressing seizures. It might have been hoped that as the use of these drugs became widespread a rational approach to the treatment of epilepsy would have developed. Although many advances have been made, particularly in the appreciation of the importance of serum anticonvulsant level monitoring (Reynolds, 1980), many unsatisfactory aspects of the drug treatment of epilepsy remain. Reynolds (1978) has identified three areas of particular difficulty which will be considered further here.

a. Choice of Drug

Amongst the drugs listed in table 1:3 there are four that would now be considered first line treatments for epilepsy. Although the use of phenobarbitone is probably declining it remains popular, particularly in France and the United States, and in view of its cheapness remains an important drug for developing countries. In Britain phenytoin has traditionally been the drug of choice, whilst Scandanavian countries have favoured carbamazepine. Despite recent worries concerning the hepatotoxicity and possible teratogenic effects of sodium valproate it is likely to remain a major drug for the treatment of epilepsy (Dreifuss, 1983).

There are few specific indications in determining the drug of choice in epilepsy. Ethosuximide and sodium valproate are the drugs of choice for the treatment of childhood abscence seizures (Loiseau, 1984; Fromm & Crumrine, 1986), the other major anticonvulsants being less effective in patients with this seizure type. Clonazepam has been found to be useful in controlling post anoxic myoclonus (Chadwick et al. 1984). For the great majority of patients with either partial or generalised epilepsies, either idiopathic or symptomatic, there is remarkably little reliable evidence as to the comparitive efficacy or

toxicity of the major antiepileptic drugs. The most important reason for this has probably been deficiencies in the design and analysis of anticonvulsant trials.

i. The Design of Anticonvulsant Trials

Coatsworth (1971) has surveyed the published literature, basing his analysis on 120 anticonvulsant trials. Of these only two were found to have used a double blind random allocation of drugs and appropriate statistical assessment. Amongst the conclusions he stated that ... "sufficient studies are not found in the literature to confidently test the relationship between the use of a drug and its influence on a particular seizure type".

Eleven years later Gram et al (1982) were able to review fifty one randomised double blind studies in epilepsy. These authors, unfortunately, reached a similar conclusion. The deficiencies in study design identified included failure to employ a washout period, marked heterogenecity amongst patient groups and short duration of follow up. Evaluation was further complicated because the majority of studies were "add on" with concurrent treatments being changed during the course of the trial. This method is also likely to lead to unpredictable drug interactions and also promotes unnecessary polytherapy. In a review of one hundred and fifty five trials of phenytoin and

carbamazepine, Shorvon et al (1981) emphasised the difficulty in making appropriate comparisons between drugs on the basis of a reduction in seizure frequency measured over short periods of time.

ii. Trials of Monotherapy in Newly Diagnosed Epilepsy

Many of the difficulties arising from the design of anticonvulsant trials discussed above can be overcome by comparing the drugs, given as monotherapy, in newly diagnosed previously untreated epilepsy. The use of monotherapy allows a comparison of efficacy to be made between individual compounds and avoids the difficulties that arise from unpredictable drug interactions. Following randomisation patients are followed up in parallel with no need to employ a cross over or wash out period. Perhaps most importantly because the drugs are given at the onset of treatment it is possible to compare their action during this crucial period of the natural history of epilepsy when the majority of remissions occur. The need to assess outcome in terms of arbitrary reductions in seizure frequency is also avoided.

Following the initial report by Reynolds et al (1976) a number of trials of monotherapy in newly diagnosed epilepsy have been undertaken. They are summarised in Table 1:4. The

TABLE 1:4 TRIALS OF MONOTHERAPY IN NEWLY DIAGNOSED EPILEPSY.

Author	Drugs	No of Patients	Follow-up, mean(range) months	Seizure Control (%)
Reynolds et al, 1976 Shorvon et al, 1978 Shorvon & Reynolds, 1982	DPH/CBZ	94	24(13-33)	50
Feely et al, 1979	DPH	13	NS	69
Stranjord & Johannessen, 1980	CBZ	24	>7	83
Feely et al, 1982	STH	10	14(7-22)	80
Turnbull et al, 1982 +	VPA	43	>12	58
	DPH	45		58
Ramsay et al, 1983 +	DPH	35	NS(6-24)	66
	CBZ	35		63
Callaghan et al,1985 +	DPH	58	NS(14-24)	67
	CBZ	59		37
	VPA	64		53
Mattson et al, 1985 +	CBZ	155	NS(12-72)	47
	DPH	165		38
	PB	155		36
	PRMD	147		35

DPH = phenytoin. CBZ = carbamazepine. STH = sulthiame.
VPA = sodium valproate. PB= phenobarbitone. PRMD = primidone.
NS = not stated.

\+ Randomised Studies

earlier studies were either nonrandomised or based on small numbers of patients. Outcome has usually been analysed by comparing the percentage of patients remaining completely seizure free after starting treatment. Those with more prolonged follow up (Shorvon & Reynolds 1982; Mattson et al, 1985) have, in general, shown higher relapse rates on treatment.

Four studies using a random allocation of the initial drug in adult epilepsy have now been published. Turnbull et al (1982) compared sodium valproate and phenytoin in 88 previously untreated newly diagnosed epileptic patients who were followed for at least twelve months from the time of randomisation. Treatment failure was defined as the occurrence of unacceptable side effects or continuing seizures despite a maximum tolerated dose. Both drugs were equally effective in controlling tonic clonic seizures. Although the percentage of patients with partial seizures who remained seizure free was equal for both phenytoin and sodium valproate there were twice as many treatment failures in patients taking the latter drug. Ramsay et al (1983) in a double blind randomized study compared phenytoin and carbamazapine as initial therapy in 70 adult patients. Thirty six percent of patients on carbamazapine and 40% of those taking phenytoin were lost to follow up and the remaining patients were only followed for 6 months. Both drugs were equally effective.

Callaghan et al (1985) have reported a trial in which 181 adults were randomised to treatment with phenytoin, carbamazepine or sodium valproate. Twenty one patients failed on treatment which was defined as failure to obtain at least a 50% reduction in seizure frequency despite anticonvulsant levels in the upper optimum range. After a follow up of 24 months polytherapy was needed in only 6 patients. The authors concluded that all three drugs were highly effective in controlling generalised seizures but less so in those who had partial seizures. It appears, however, that the percentage of patients with complete seizure control was considerably higher for those receiving phenytoin (see table 1:4), and this was particularly so in those with generalised seizures. This observation is at variance with other studies and was not commented upon by the authors.

The most extensive investigation to be published has been the Veterans Administration multi-centre trial (Mattson et al, 1985). In this study primidone, phenobarbitone, phenytoin and carbamazapine were compared in 421 adults with epilepsy who were followed for at least two years or until the time of treatment failure. It appears that nearly one half of the patients did in fact receive some form of treatment before randomization and 32% were lost to follow up. Overall treatment success was highest with phenytoin and carbamazapine, intermediate for

phenobarbitone and lowest with primidone. All the patients had serum anticonvulsant levels in the therapeutic range, regardless of seizure control. In those with continuing seizures, the dosage was increased until toxicity occurred. Amongst the 223 treatment failures, only 11 were due to seizures alone, the rest arising from drug toxicity with or without uncontrolled seizures. The main conclusions to arise from the study appear to be more a reflection of acute side effects arising from the drugs, rather than their comparative efficacy. Some information, however, was given regarding seizure control. There was no difference between the drugs in patients with tonic clonic seizures. In those patients with partial seizures 43% remained completely seizure free amongst those who were taking carbamazapine. The outcome was significantly better than those randomised to primidone, phenobarbitone or phenytoin where the corresponding results were 15%, 16% and 26% respectively.

It is apparent that there are methodological difficulties in each of these studies. These include small numbers of patients, inadequate follow up, inappropriate statistical assessment and the occurrence of toxicity as a major cause of drug failure. The results from these initial studies do suggest that there may be no difference between the major anticonvulsants in their ability to control tonic clonic seizures. It is possible, however, that patients with

partial seizures do not respond in the same way with carbamazapine being more effective than sodium valproate. This is an important observation since it is this group of patients in whom seizures are most difficult to control. The design and undertaking of these trials call for a considerable dedication of time and resources. Unlike cross over studies undertaken over short periods of time in chronic epileptic patients recruitment must continue over a number of years and prolonged follow up is needed. The results from these initial trials, despite the methodological problems outlined above, are for the first time giving some indication as to the comparative efficacy of the major anticonvulsant drugs.

b. Polytherapy

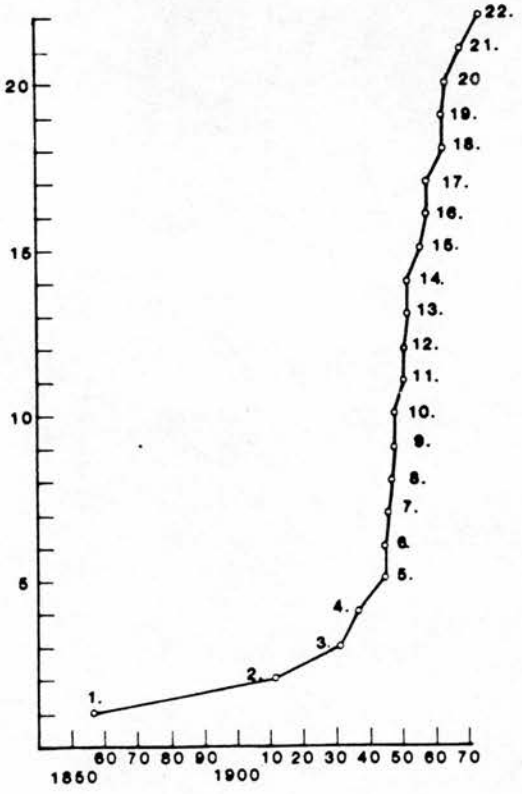
The number of different treatments that have been used in epilepsy is enormous. In the historical literature, considered in the previous section, it was shown that many of these were based on erroneous theories as to the causes of epilepsy and others were either highly toxic or of dubious efficacy. Following the introduction of bromides large number of drugs have been shown to be effective in treating epilepsy. These have been discovered either by serendipidy, the screening of new compounds in animal models of epilepsy, or predictions of efficacy made on the basis of chemical struture. The discovery of novel

anticonvulsant drugs has accelerated in recent years as compounds are developed that act directly on inhibitory and excitatory neurotransmitters (Meldrum, 1983). The cumulative increase over recent years in new antiepileptic drugs is shown in Figure 1:1. This graph is by no means exhaustive and does not include the many compounds that have been tested but failed to gain widespread usage.

In the face of such lage numbers of anticonvulsant drugs it is not supprising that polytherapy continues to be widespread. In a study of the drugs taken by 11,720 epileptic patients in four European countries it was found that the average number of drugs per patient was 3.2, of which 84% were anticonvulsants. Only 4% were taking a single drug, 30% were taking two drugs and the remaining two-thirds were receiving three or more medications (Guelen et al, 1975). One patient was found to be taking twelve different types of drugs! The majority of the patients in this study were treated in Scandinavia but there is little reason to suppose that treatment policies are any different in other westernised nations.

The disadvantages of polytherapy have now become more widely appreciated (Reynolds & Shorvon, 1981). There is remarkably little evidence that combinations of drugs are

FIGURE 1:1 CUMMULATIVE INCREASE IN ANTIEPILEPTIC DRUGS AVAILABLE TO THE MEDICAL COMMUNITY. (from Friedlander, 1986)



Horizontal Axis:
Year of Introduction

Vertical Axis:
Cummulative Number of Drugs

Key to Drugs in Figure 1:1 and Date of First Report

1.	Bromide	1857	13	Primidone	1952
2.	Phenobarbitone	1912	14	Methsuximide	1952
3	Methobarbitone	1932	15	Ethotoin	1956
4.	Phenytoin	1937	16	Aminogluteth-emide	1958
5.	Trimethadione	1945	17	Ethosuximide	1958
6.	Mephenytoin	1945	18	Diazepam	1963
7.	Paramethadione	1946	19	Carbamazepine	1963
8.	Phethenylate	1947	20	Valproic Acid	1964
9	Phenacimide	1948	21	Clonazepam	1969
10	Methabarbitone	1948	22	Chlorazepate Dipotassium	1974
11	Benzchlorprop-amide	1951			
12	Phensuximide	1951			

any more effective in controlling seizures than a single drug given in optimum dosage. This is particularly so when patients are on polytherapy and all the anticonvulsant levels are below the therapeutic range. The use of polytherapy, often in assosciation with complicated dosaging regimes, can increase the probability of poor compliance (Terrence & Alberts, 1978). Unpredictable drug interactions can occur and precipitate acute anticonvulsant toxicity (Perrucha, 1982). Side effects may be additive, particularly when sedating drugs such as barbiturates and benzodiazepines are used together, leading to drowsiness and behaviour disorders (Theodore & Porter, 1983). Perhaps the most striking evidence against polytherapy is the improvement that can occur in a substantial number of patients following drug reduction.

Shorvon and Reynolds (1979) have reported a two year prospective study in 40 adult outpatients with chronic epilepsy. The mean number of drugs was reduced from 2.1 to monotherapy in 29 patients. Amongst these 29, seizure control improved in 16 (55%), was unchanged in 8 (28%) and deteriorated in only 5 (17%). These findings have now been confirmed by a number of other investigators (Table 1:5). In the study by Albright & Bruni (1985) few clinical details concerning the outcome were given. In the remaining studies all have shown that between a third and three-quarters of patients experienced an improvement in

TABLE 1:5 STUDIES OF POLYTHERAPY REDUCTION. THE PERCENTAGE OF PATIENTS WITH IMPROVED SEIZURE CONTROL FOLLOWING DRUG REDUCTION.

Author	Number of Patients	Drugs Reduced	Follow up (months)	Improved Control N(%)
Callaghan et al, 1978	17	17	14	9 (53)
Shorvon & Reynolds, 1979	40	29	12	16(55)
Maheshwari & Padmiri 1981	152	152	NS	119(78)
Schmidt, 1983	36	36	12	13(36)
Theodore & Porter, 1983	69	69	6	43(62)
Callaghan et al, 1984	35	29	NS	19(54)
Lesser et al, 1984	28	28	>3	15(54)
Albright & Bruni, 1985	90	72	16	10(14)

seizure control after reduction of polytherapy for periods ranging from 3 to 16 months.

In a proportion of patients it was difficult to reduce polytherapy because of an exacerbation of seizures that occurred during the period of drug withdrawal. This has been reported to be a particular problem when barbiturates or benzodiazepines are discontinued (Schobben 1979). Shorvon and Reynolds (1979) found that it was impossible to reduce polytherapy in 11 out of 40 patients (28%) and similar figures were reported by Lesser et al (1984). Schmidt (1983) however, was able to reduce polytherapy successfully in all his patients and attributed this to slow anti-convulsant withdrawal. Although few details were given it appears that most patients' drugs were reduced over a period of 2 ot 20 weeks, which is in fact in broad agreement with the policy of other authors. Similarly Theodore & Porter (1983) did not experience this problem in any of their patients, although in this study three-quarters of cases were admitted to hospital and drugs were reduced only to a mean of 1.7 per patient.

The benefits of drug reduction are not restricted to improvements in seizure control. Shorvon & Reynolds (1979) reported improvement in mental functions, particularly alertness, mood and sociability in 53% of patients following reduction of polytherapy. Theodore & Porter

(1983) only withdraw sedating drugs, viz. bromides, barbiturates and benzodiazepines. They reported evidence of reduced toxicity, particularly ataxia and nystagmus. Patients also appeared more alert and there was a lower incidence of behaviour disorders. Thompson and Trimble (1982) carried out a battery of neuropsychological evaluations in 20 patients with chronic epilepsy in whom drugs were reduced from a mean of 2.8 to 1.6 per patient. Marked improvement in mood and cognitive function occurred, particularly in those tests which appeared to measure speed of mental processing.

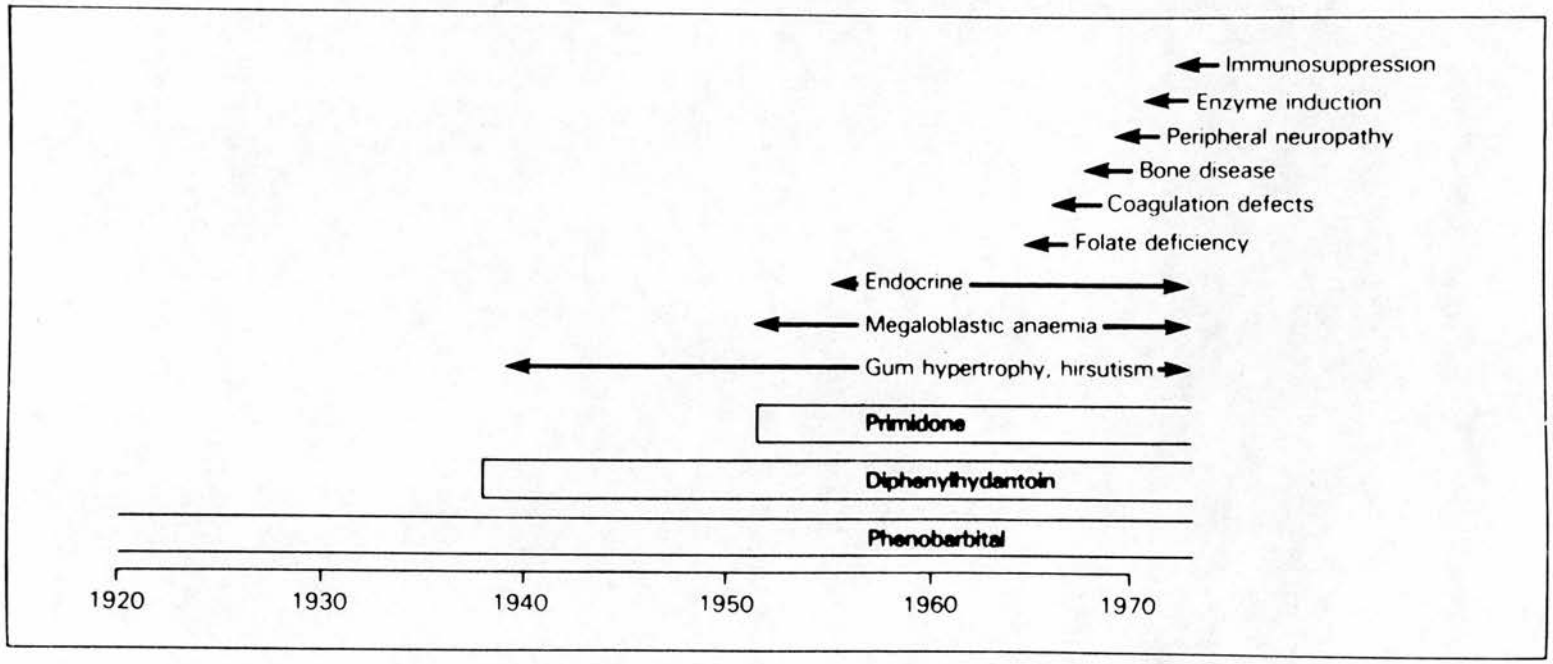
c. Chronic Toxicity

Patients with epilepsy are particularly prone to the chronic toxic effects of medication. The drugs affect a wide variety of metabolic pathways and cause both idiosyncratic and dose related side effects (Reynolds, 1975). In patients who have intractable seizure disorders, treatment is given in high doses, often as a combination of drugs. There can be no other group of patients who are subjected to such a large number of potentially toxic drugs throughout the period of a lifetime. Because epilepsy is commonest in children, three-quarters of cases occurring before the age of 20 years, particularly worries exist as to the possible adverse effects on growth and development.

The ability of phenytoin to cause chronic changes in connective tissue, particularly gum hypertrophe, was recognised shortly after its introduction, (Kimball, 1939). It is curious, however, that many of the chronic side effects of barbiturates and hydantoins were not recognised until many decades after their introduction. Reynolds (1975) has reviewed the chronic toxicity of antiepileptic drugs, listing their diverse side effects under nine main headings. Figure 1:2. shows the delays that have occurred in the recognition of such important toxic effects as folate deficiency, metabolic bone disease and encephal-opathy. It is likely that further chronic side effects will be discovered, particularly following the prolonged usage of newer drugs such as sodium valporate and carbamazepine.

Phenytoin has a number of neurotoxic effects. Cerebellar dysfunction was reported shortly after its introduction and has been reported to be irreversible (Reynolds, 1975; Dam, 1982). It is now well recognised that phenytoin can cause dyskinaesias and peripheral neuropathy (Trimble & Reynolds, 1984). Glaser (1972) has described a chronic or subacute encephalopathy where signs of disturbed mental functioning may be associated with worsening seizure control and focal neurological signs which are reversible when the drug is withdrawn. The syndrome is associate with marked slowing of the EEG

FIGURE 1:2 TIME TAKEN TO RECOGNISE CHRONIC TOXIC EFFECTS OF BARBITURATE AND HYDANTOIN ANTICONVULSANTS (from Reynolds, 1975)



(Roseman, 1961) and can occur with anticonvulsant levels within the accepted therapeutic range.

An area of particular importance is the effects of anticonvulsants on cognitive function. Lennox (1942) listed drugs as a possible cause of mental decay, along with other factors such as heredity, brain injury antedating the onset of seizures, psychological handicaps and the seizures themselves. Trimble and Reynolds (1976) subsequently reviewed the published literature on psychological function in relation to anticonvulsant drugs and concluded that many, but not all, of the studies had shown that medication had an adverse effect on mental processes. Often the effects were subtle and appropriate psychometric assessments have been developed to detect them. When given to normal volunteers for periods of up to one month, phenytoin, carbamazepine, sodium valporate and clonazepam have all been shown to impair cognitive function in a dose dependent manner with anticonvulsant levels within the optimum range (Thompson & Trimble, 1982). It also appears that there may be important differences between the drugs (Dodrill and Troupin, 1977; Reynolds, 1983; Andrewes et al, 1986). In a recent long term prospective evaluation of psychometric functioning in children with epilepsy, Bourgeois et al (1983) concluded that the number of drugs to which the patient had

experienced toxic reactions was the best predictor of outcome in those patients in whom intelligence quotient deteriorated.

E. THE PROGNOSIS OF EPILEPSY

The prognosis of patients with epilepsy can be considered under three broad headings. Firstly, the prognosis of patients who present with a single seizure. This group give rise to a common clinical dilemma and because they are often untreated are of particular interest to the subject of this thesis. Secondly the prognosis of patients in whom the illness has become established. This is, by definition, the outcome in those patients who have experienced two or more attacks and relates largely to the long term response to treatment. Finally, the prognosis following anticonvulsant withdrawal. This important aspect has received only scant attention until comparitively recent years and will be reviewed in the final section. The literature considered here deals primarily with seizure relapse and seizure control rather than the cognitive, psychological and social difficulties that can complicate the course of epilepsy.

1. PROGNOSIS FOLLOWING A FIRST SEIZURE

a. Historical Literature

It has long been appreciated that following the first seizure the tendency towards further attacks will remain. Areteus (quote by Temkin, 1971, page 42) stated that the

isolated paroxym was an acute affliction. More often than not, however, it would repeat itself and the disease take on a chronic form; consequently after the cessation of the first attack, the physician would still suspect its latent presence within the body. A similar sentiment was expressed by Gowers. On the opening page of "Epilepsy and Other Chronic Convulsive Diseases" he states:

> "When one attack has occurred, whether in apparent consequence of an immediate excitement or not others usually follow without any traceable cause... If an individual suddenly has an epileptic convulsion for the first time, for which no cause can be discovered, central or peripheral, it is probably the commencement of epilepsy".
>
> (Gowers, 1881)

He went on to say that there was no means of discovering, on any considerable scale, the proportion of patients who might experience only one seizure. He did, however, give an analysis of the intervals between the first and second seizures in a series of 160 patients (Table 1:6). The second seizure followed the first within a month in one third of cases, within a year in a further third and exceeded one year in the remaining one third. Occasional cases were seen where the two seizures occurred decades apart.

It is curious that since the time of Gowers' work, there has been remarkably little study of this important aspect

TABLE 1:6 INTERVALS BETWEEN THE FIRST AND SECOND SEIZURES IN 160 CASES OF EPILEPSY (Gowers, 1881)

Less than 1 week	18	55 cases under one month.
1 week to 1 month	37	
1 month to 3 months	13	
3 months to 6 months	21	52 cases more than a month
6 months to 1 year	18	and less than a year.
1 year to 2 years	18	
2 years to 3 years	6	
3 years to 5 years	7	53 cases more than a year
Over 5 years	22	

viz.

6 years	3 cases
7 years	9 cases
8 years	1 case
10 years	3 cases
11 years	1 case
14 years	1 case
16 years	1 case
18 years	2 cases
20 years	1 case

of the natural history of epilepsy until very recent years. Williams (1975), in his lecture on "The Borderlands of Epilepsy Revisited" considered the single seizure to be an isolated event of little significance. Livingstone (1958) reported in a review his experience with 200 children with a single seizure but this work was apparently never fully published.

Our current understanding of the subject has been derived from two main sources. Firstly from the epidemiology of epilepsy. Although community surveys have rarely examined the early prognosis of epilepsy in detail, a number of them have attempted to identify from an unselected population the proportion of patients who experience only a single attack. Secondly a number of prognostic studies have been undertaken in recent years examining the probability of seizure recurrence in groups of patients presenting with a single seizure either in the community or to hospital outpatients or EEG departments.

b. Epidemiological Surveys

Only 8 epidemiological surveys have, in addition to identifying cases of epilepsy, included patients with only a single seizure (Table 1:7). The methods of case ascertainment in all of these have differed widely. Mathai et al (1968) conducted a field survey amongst the

TABLE 1:7 EPIDEMIOLOGICAL SURVEYS OF PATIENTS WITH SINGLE SEIZURES.

Author	Number	Single Seizures N(%)	Recurrent Seizures N(%)
Costeff, 1965 *	26	13(50)	13(50)
Mathai et al, 1968	32	8(25)	26(75)
van den Berg & Yerushalmy, 1969 +	113	40(35)	73(65)
Hauser & Kurland, 1975	922	214(23)	708(77)
Blom et al, 1978 *	74	30(40)	44(60)
Goodridge & Shorvon, 1983	122	22(18)	100(82)
Hirtz et al, 1984 +	512	199(39)	313(61)
Juul-Jensen & Foldspang, 1985	1270	202(16)	968(84)

* Childhood epilepsy
\+ Based on the follow-up of a cohort of live births

Chomorro people on the Marina Islands. Because of communication difficulties, due to cultural and language differences, only those who had experienced major seizures were identified. Two of the surveys (Van den Berg & Yerushalmy, 1969; Hirtz et al, 1984) were follow-up studies of a cohort of live births up to the ages of 5 and 7 respectively. Although not strictly undertaken as epidemiological surveys they have been included here as both were based on identification of cases from an unselected sample of the population. Prospective evaluation was used and detailed documentation of clinical characteristics were given, particularly in the latter study. The remaining three studies have been retrospective analyses based on general practioner records in South East England (Goodrige & Shorvon, 1983) and a continuous register of cases in Rochester, Minnesota (Hauser & Kurland, 1975) and Greater Aarhus, Denmark (Juul-Jensen & Foldspang, 1983). Three studies included patients who experienced seizures in association with acute central nervous system disorders, head injury or alcohol withdrawal (Blom et al, 1978; Hirtz et al, 1984; Goodrige & Shorvon, 1983).

Despite these methodological differences there appears to have been good agreement that in 60% to 80% of cases identified from an unselected population, seizures are likely to be recurrent. The higher recurrence rate reported by three of the authors (Hauser & Kurland, 1975; Juul-Jensen

& Foldspang, 1983; Goodridge & Shorvon, 1983) may be due to the retrospective nature of the survey. Such studies may miss milder cases and those with single seizures. Only in the study by Hirtz et al (1984) were any details given concerning the timing of the occurrence of the second seizure or of the factors that were thought to be of prognostic significance. These authors found that following the first afebrile seizure the second followed within a six months in 74%, by one year in 87% and by two years in 96%. Children with neurodevelopmental abnormalities were not any more likely to experience recurrent seizures. Curiously those patients with an initial symptomatic seizure had a lower recurrence rate, possibly because patients with seizures arising as a cause of acute trauma, toxic encephalopathy and electrolyte disturbances were included.

c. Follow up Studies of Patients presenting with a Single Seizure

i. Seizure Recurrence

The results of the nine prognostic studies of patients presenting following a first seizure are summarised in Table 1:8. The highest recurrence rate was reported by Johnson et al (1972) who studied 77 enlisted navy personnel who were admitted to hospital with the complaint of a "single

TABLE 1:8. PROGNOSTIC STUDIES OF PATIENTS PRESENTING WITH A SINGLE SEIZURE

Author	Number of Patients	Follow-up Mean(Range) months	Percent Recurrence
Thomas, 1959	42	NS(42-102)	27
Johnson et al, 1972	77	36	64
Saunders & Marshall, 1975	33	26(10-48)	33
Cleland et al, 1981	70	57(36-120)	39
Hauser el al, 1982	244	12	16*
		24	21
		36	27
Todt et al, 1985	179	12	59
Camfield et al, 1985	168	NS	52
Annegers et al, 1986	380	12	36 *
		36	48
		60	56
Hopkins et al, 1988 +	100	12	39 *
		24	49
		36	52

* Actuarial estimates
+ Patients seen within one week of an initial seizure

convulsion, seizure or unexplained loss of consciousness." Although a recurrence was reported in 49 (64%) it appears that in 19 of these the final diagnosis was either a psychiatric illness, syncope or some other disorder. As the most important prognostic factors were an initial history suggesting a seizure, post ictal confusion and epileptiform abnormalities on the EEG, it appears that the development of epilepsy was most strongly related to the initial event indeed being a seizure. If those patients in whom the diagnosis were in doubt were excluded the recurrence rate fell to 39%.

Four of the studies (Thomas, 1959; Saunders and Marshall, 1975; Clelland et al, 1981; Hauser et al, 1982) have all reported that seizures recurred in around one third of patients. In the largest of these Hauser et al (1982), studied 244 patients who were seen in a hospital clinic over a four year period following a first ever "unprovoked" seizure. Patients with a seizure related to systemic metabolic dysfunction, acute neurological insult or alcohol withdrawal were excluded. Patients with a past history of such seizures and who subsequently had an apparently unprovoked attack were, however, included. Four hundred and thirty five patients were ineligible because they had experienced two or more seizures at the time of first diagnosis. The cumulative probability of seizure recurrence was 16% at 12 months, 21% at 24 months and 27% by 36 months.

The studies by Thomas (1959), Saunders & Marshall (1975) and Cleland et al (1981) were based on patients attending EEG or neurology outpatient departments and it is likely that a similar form of patient selection occurred with patients who experienced an early recurrence being excluded.

More recent studies have reported higher recurrence rates of between 50% and 60%. Todt et al (1985) studied 179 children who were seen in an EEG department within two weeks of a first ever tonic clonic seizure. None of the patients was treated. The reported recurrence rate of 59% may well have been an underestimate as those patients who experienced a recurrence after the first year of follow up were apparently excluded.

Camfield et al (1985) reported that the recurrent rate in 168 children who were referred to an EEG department following a single afebrile seizure was 52%. The study was retrospective and no indication of the time for which patients were followed from the time of the first seizure was given. Although it was claimed that patients were likely to come from an unselected population, 94% were in fact referred by paediatricians and neurologists. It is likely therefore that there was a considerable delay between the first seizure and inclusion in the study as 141 patients had experienced more than one attack before an EEG was performed.

The study by Annegers et al (1985) is of interest as it is the only one that has been community based. The records linkage system of the Mayo Clinic was used to retrospectively identify 849 individuals as having "potentially an initial seizure" whilst residents in Rochester, Minnesota between 1935 and 1979. Four hundred and twenty five patients who had experienced multiple attacks were excluded from the analysis. Although the record system apparently included all in-patients, out-patients, casualty attendances and home visits the proportion which were identified from either hospital or community sources was not given. It is unfortunate that further details on case selection were not provided as the age structure of the population was unusual. Fifty-eight per cent were apparently aged 55 or over at the time of the first seizure. A further difficulty is that no mention was made of the methods used to validate the diagnosis, which is likely to be of importance in a retrospective study spanning a period of 50 years. Unlike other studies, however, appropriate actuarial statistical methods were used.

Hopkins et al (1988) have recently reported a multicentre study of 408 adults presenting to a neurology outpatients departments with a single seizure. Patients with seizures occurring in the context of acute precipitating factors such as alcohol were included and 31 patients were treated

following the first attack. The cumulative probability of seizure recurrence by four years was 45% for males and 46% for females. The total number of patients excluded because they had epilepsy when first seen was not stated but 25 subjects had their second seizure after referral but before attending the outpatients department. In those patients seen within one week and eight weeks the recurrence rates were 52% and 22% respectively.

Most of the studies are in agreement that the majority of recurrences occur within one year of the first seizure (see Table 1:9). The lower figures reported by Cleland et al (1981) and Hauser et al (1982) may be due to the fact that many patients who experienced an early relapse were excluded. Camfield et al (1985) and Johnson et al (1972) reported that three-quarters of patients who went on to develop epilepsy did so within one year and it appears that late relapses were uncommon. Annegers et al (1986) found that in 117 subjects who remained seizure free for at least five years only 7 of them subsequently experienced a recurrence.

ii. Prognostic Factors

There has been little systemic study of the prognostic factors that are of importance in determining recurrence rates following a first seizure. In the earlier studies

TABLE 1:9. PROGNOSIS FOLLOWING A FIRST SEIZURE. THE PERCENTAGE OF PATIENTS EXPERIENCING A RECURRENCE BY ONE YEAR OF FOLLOW UP

Author	Recurrence rate by One Year of Follow-up (%)	Total Recurrence Rate (%)
Johnson et al, 1972	49	64
Cleland et al, 1981	20	39
Hauser et al, 1982	16	27
Camfield et al, 1985	40	52
Todt et al, 1985	59	59 *
Annegers et al, 1986	36	56
Hopkins et al, 1988	39	52

* All patients followed for one year

listed in table 1:8 the documentation of patients was generally poor and the total numbers insufficient to give clear guidance. Patient selection, differing treatment policies and innapropriate statistical analysis also make interpretation of the results difficult.

There is, however, a degree of agreement that patients with symptomatic seizures or associated neurological handicaps have a higher recurrence rate. Annegers et al (1986) found that amoung 287 patients with idiopathic seizures the recurrence rate by 5 years was 45%, compared to 77% for the remaining 122 patients in whom a cause was established. Those with neurological deficits present since birth had a particularly bad outcome with 92% developing epilepsy. A similar finding has been reported by Todt et al (1985). Patients with post natally acquired neurological handicaps have also been reported to have a worse prognosis (Camfield et al, 1985; Todt et al, 1985; Annegers et al, 1986).

Because it is unusual to present folowing a single partial seizure some authors have specifically excluded patients with this particular seizure type. Camfield el al (1985) found that amoungst 168 children who were referred to an EEG department 19 had complex partial seizures. In this group the recurrence rate was significantly higher than in those with tonic clonic seizures. Hauser at al (1982), however, found that seizure type was not significantly associated

with outcome. Patients with symptomatic seizures were excluded from the analysis and the clinical material was unusual in that 47 presented following a single simple partial seizure compared with 18 in whom the initial attack was a complex partial seizure. Annegers et al (1986) reported that patients with partial seizures had a higher recurrence rate but the numbers with this seizure type were not given.

The importance of the initial EEG as a useful prognostic indicator is disputed. In the study by Annegers et al (1986) only a third of patients had this investigation performed which may have led to bias in the results. Hauser et al (1982) reported that a small subgroup of 13 patients with generalised spike and wave the recurrence rate was higher but other features of the initial EEG was of little use in predicting outcome. Using a broader definition Cleland et al (1981) found that the recurrence rate was higher in those in whom the EEG was abnormal compared to those in whom it was normal. Similarly Todt et al (1985) reported that the recurrence rate was 59% in those with normal EEGs compared to 73% in those which showed epileptiform abnormalities.

iii. Treatment

The percentages of patients who were treated following the first attack are summarised in Table 1:10. It is apparent that there has been little agreement on this aspect of patient management. There is tendency for the more recent North American authors to report that as many as two-thirds of patients were given medication (Hauser et al, 1982; Camfield et al, 1985; Annegers et al, 1986). In none of the studies, however, were any details given as to the period of time for which the drugs were taken. Poor compliance, which is likely to have been widespread, was not commented upon. It is difficult to detect any impact that treatment may have had on seizure recurrence from the studies shown in table 1:10. In the study by Annegers et al (1986) the recurrence rate appears to have been considerably higher in those patients who were given medication (60% vs. 41% for those patients who were not treated). Other authors have reported no significant difference in outcome (Hauser et al, 1982; Hirtz et al, 1984; Camfield et al, 1985). Selection bias may have been of considerable importance as it is likely that patients who were thought to be at higher risk of developing epilepsy were more likely to be treated (Tucker & McJunkin, 1984).

TABLE 1:10. PROGNOSTIC STUDIES OF PATIENTS PRESENTING WITH A SINGLE SEIZURE. PERCENTAGES OF PATIENTS TREATED FOLLOWING THE FIRST SEIZURE

Author	Number of Patients	Patients treated N(%)	Recurr rate (%)
Johnson et al, 1972	77	none	64
Saunders & Marshall, 1975	33	none *	33
Cleland et al, 1981	70	none *	33
Hauser et al, 1982	244	168(69)	27
Hirtz et al, 1984	512	138(27)	61
Camfield et al, 1985	168	115(68)	52
Todt et al, 1985	179	none	59
Annegers et al, 1986	424	257(61)	56
Hopkins et al, 1988	306	41(13)	45

* Unstated number of patients receiving treatment excluded from the study

2 THE PROGNOSIS FOR SEIZURE CONTROL IN EPILEPSY

a. Historical Literature

The earliest reference to the prognosis of patients with epilepsy is be found in the Hippocratic writings (Tekin, 1971 pages 45 et seq.). Epilepsy dating from birth was thought to be incurable. If, however, it began before puberty it might cease around that time. Epilepsy that started in adolescence had a worse prognosis, although even here cures could be obtained. Epilepsy that began after the age of 25 lasted until death, and the occurrence of seizures in the elderly was often fatal. The Hippocratic view of prognosis was, therefore, rather gloomy, although it was recognised that the prognosis could be better in cases arising in childhood.

The prognosis was particularly poor if the disease had taken on a chronic form. Areteaus stated: "but if the mischief lurk there until it strike root, it will not yield even to the physician or the changes of age, so as to take its departure, but lives with the patient until death". It was therefore of great importance to treat the disease before it became chronic, a view that was also expressed by Hippocrates (Temkin, 1971 page 65).

During the Eighteenth Century the movement by Pinel in France and Tukes in England led to humanization of the treatment of the insane. This benefitted those suffering from epilepsy as they had often been incarcerated together. During the first half of the Nineteenth Century special wards were established within asylums for the insane for those patients suffering from epilepsy. This subsequently led to the setting up of separate institutions for those with epilepsy, such as the National Hospital for the Paralysed and Epileptic, Queen Square, London in 1860. There was a rapid increase in knowledge about epilepsy and for the first time statistical assessments based on the observation of large numbers of patients were undertaken. A number of important monographs such as those by Tissot, Delasiauve, Esquirol, Reynolds and at a later date Gowers were published.

This increase in knowledge was not unfortunately accompanied by any general agreement as to the prognosis of epilepsy. Reynolds (1861) opens his chapter on prognosis by quoting the opposing views of Tissot and Delasiauve:

> "J'en ai gueri un tres grand nombre". (Tissot, 1770)
> "Elle conduit presque infailliblement a l'incurabilite par de lentes degradations". (Delasiauve, 1854)

Reynolds (1861) gave the results of treatment in eighty one cases, of whom eight recovered completely. Recovery was

defined as perfect restoration of health which lasted for at least four years. Esquirol at the Salpietriere subjected thirty patients each Spring and Autumn to some new treatment. The results were not promising:

"Toujours une nouvelle medication suspenduit les acces pendant quinze jours; chez les unes pendant un mois; deux mois chez autres et meme pendant trois mois. Apres ce terme les acces reparaissent sucessivement chez toutes nos femmes..... je n'ai pu obtenir de guerison".

(Esquirol E, 1838. Quoted by Reynolds, 1861)

In marked contrast to Esquirol, Delasiauve and Reynolds, Herpin believed the prognosis was good.He based his work on three hundred patients who attended his private clinic. His books were widely quoted both by Gowers and Hughlings Jackson. He is probably best remembered for his work on Epileptic Auras and in particular defining minor seizures or "Acces Incomplete". His other major work "du Prognostic et du Traitment Curatif de l'Epilepsie", in itself had an optimistic title. He advocated the use of zinc oxide in the treatment of epilepsy.

"Que la medecine peut intervenir utilement chez les trois quarts des malades; qu'elle peut en guerir plus de la moitie, et procurer une amelioration plus ou mois durable dans un cinquieme des cas; enfin que le nombre des epilepsies rebelles aux traitements diriges avec perseverance est d'un quart seulement".

(Herpin, 1852 quoted by Temkin, 1971)

Herpin believed that it was possible to treat three quarters of cases satisfactorily. His results, however, were subject to scathing criticism by Delasiauve on the basis of incorrect diagnosis in many patients, doubts as to the soundness of his cure and also the inclusion of patients who had experienced only a single seizure. A note of caution was introduced into the controversy by Marshall Hall (Temkin, 1971). He admitted that cases of epilepsy due to diseases within the cranium were often incurable. These were the cases frequently met with in institutions, and hence observers of the disease who gathered their material at such places inclined to the belief that epilepsy could not be cured. This controversy surrounding prognosis in epilepsy has continued for almost a century and curiously the solution proposed by Marshall Hall may be equally relevant today.

b. The Introduction of Modern Anticonvulsant Drugs

During the second half of the Nineteenth Century a major therapeutic advance occurred with the discovering of bromides. All authorities agreed this drug had a very considerable impact on the treatment of epilepsy. This was followed in 1912 by the introduction of phenobarbitone (Hauptmann, 1912) and subsequently by phenytoin (Merritt et al, 1938). As these drugs gained widespread usage a number of reports were published giving experience of their usage in large number of patients. Arieff (1951) summarised his

experience in 311 patients seen over a twelve year period. The use of bromide or phenobarbitone, alone or in combination, led to remissions in 61% of cases and the addition of newer drugs (phenytoin and mesantoin) increased the remission rate to 68%.

Equally good results were reported for phenytoin. Merit and Putman (1938) found that in 267 cases, 54% had their seizures "completely relieved". Yahr et al (1952) reported that the use of phenytoin and phenobarbitone resulted in control or improvement of seizures in 79% of patients.

Gibbs (1947) in a review of the new drugs available to treat epilepsy stated that "the informed practionner will be able to treat successfully 75% of patients with seizures". Other authorities were equally enthusiastic. Lennox and Lennox summarised their experience as follows:

> "Considering only metabolic epilepsy, the following is doubtless an understatement: at least three fourths of patients can be relieved of at least three fourths of the seizures they would have had without drug therapy. Of these, perhaps one half will be completely free. Those with organic epilepsy will fair less well. Perhaps the proportion greatly benefitted or freed will be one half or two thirds, instead of three fourths".
>
> (Lennox & Lennox, 1960)

Livingston (1972) reported his considerable experience in treating twenty thousand epileptic children over a thirty five year period. The results were similar to those of Lennox. Sixty per cent had complete control of seizures, 25% had a significant reduction in seizure frequency or severity and in only 15% were seizures refractory to all therapeutic regimens.

c. The Work of Rodin.

In 1968 Rodin published an important critical review of the previous work on the prognosis of patients with epilepsy. His book has been very influential and his conclusions widely quoted and because of their importance they will be considered in some detail in this section.

Rodin (1968) examined the claims that 80% to 85% of patients could be controlled with medication. Rodin (1968) attributed this statement to a paper published by Yahr et al (1952). These authors found that "the use of diphenylhydantoin sodium and phenobarbital in this group of three hundred and nineteen patients resulted in seventy nine per cent control or improvement of seizures regardless of causation. The addition of other anticonvulsants added 6%, giving an overall rate of 85% improvement or control". However, as Rodin observed, further analysis of the results showed that only 48% of the patients were completely controlled for periods varying from

less than six months to five and a half years. In the remaining 37% there was an "improvement" in seizure control.

A second problem arose due to failure to take account of duration of follow up. In the study by Yahr et al (1952) a considerable proportion of patients had only been followed for periods of up to six months. A similar criticism applied to the results of Merritt and Putman (1938) and also those of Arieff (1951). Rodin (1968) emphasised that in epilepsy the course of the disorder is often one of remission and exacerbation and that statements on prognosis could not based on such short follow-up. To emphasise this point he quoted the results of Bridge (1949) who followed 472 epileptic children for periods of five years or more. Although 46% had been seizure free for six months or more with increasing follow up the remission rate fell such that only 17% had been seizure free for a total of five years or more.

Rodin (1968) stipulated that conclusions concerning the prognosis of epilepsy could only be made on the basis of prolonged follow-up. Furthermore, imprecise statements such as "improvement" or "reduction in seizure freqency" were inadequate. Only those studies which gave the proportion of patients who at the end of follow up had been completely seizure free for at least one year were considered. The results of the studies that Rodin found had met these criteria are shown in Table 1:11. It was striking that Turner

TABLE 1:11 STUDIES OF THE PROGNOSIS FOR SEIZURE CONTROL EPILEPSY. THE PERCENTAGE OF PATIENTS EXPERIENCING A TERMINAL REMISSION OF AT LEAST ONE YEAR (Modified from Rodin, 1968)

Author	Number	Minimum Duration of remission	Percent in Remission
Habermaas, 1901	937	2	10
Turner, 1907	87	2	32
Gross, 1930	125	10	11
Kirsten, 1942	174	3	22
Alstrom, 1950	897	5	22
Strobos, 1959	228	1	38
Kiorboe, 1960	130	4	32
Probst, 1960	83	2	31
Trolle, 1960	799	2	37
Juul Jensen, 1963	969	2	32
Lorge, 1964	177	2	34

in 1907 in a series from the National Hospital reported identical results using bromides to the more recent study of Juul-Jensen (1963) . In fact the best results were reported by Strobos(1959) who found that only 38% of patients were in one year remission at the end of follow up.

Rodin (1968), therefore, found little evidence to support the optimistic views that the introduction of new drugs had led to significant improvements in prognosis. For the great majority of patients epilepsy was a chronic disorder.

> "Eighty per cent of all patients with epilepsy are likely to have a chronic seizure disorder. This does not rule out short term remissions or changes in seizure pattern, it merely re-emphasises that epilepsy should be regarded as a chronic condition with remissions and exacerbations" (Rodin,1968)

In contrast to the controversy that had surrounded the long term outcome in epilepsy Rodin found that there was a reasonable degree of agreement concerning the nature of adverse prognostic factors in epilepsy. These had been identified shortly after the introduction of bromides. Gowers (1881), for example, found that patients with hemiplegic epilepsy, minor seizures or a long duration of epilepsy all appeared to respond less well to treatment. In view of their importance Rodins' main conclusions are given in full below.

"1. Approximately one third of all epileptic patients are likely to achieve a terminal remission of at least two years.

2. The percentage rises to between 50 and 60% if one considers only those patients who have grand mal seizures without associated minor attacks.

3. It drops to approximately 20 to 30 per cent if one deals with patients who have psychomotor seizures.

4. The percentages of patients who are regarded in terminal remission stand in marked indirect relationship to the length of follow up.

5. The longer the illness has lasted, the less likely will control be achieved.

6. The more seizures the patient has experienced prior to his first visit to the physician, the less likely will be complete control.

7. The more different seizure types a given patient has experienced, the less likely control.

8. The more abnormal the neurological examination, mental status examination, and the lower the IQ, the more difficult will it be to control the patient.

9. The younger the patient at the time of onset of the illness, the less likely will complete control be achieved: but there are some authors who feel that age at time of onset is not a good prognostic indicator.

10. The initial EEG is of limited value for prognosis, but a persistently abnormal EEG during treatment tends to be associated with poor seizure control. Opinions are more divided between authors on the importance of heredity, other etiological factors, nocturnal versus diurnal seizures, and sex."

Rodin (1968)

d. Subsequent Prognostic Studies in Epilepsy

A number of important prognostic studies have been published since the time of Rodin's reveiw of the literature. The results have been summarised in table 1:12. Only those studies which were based on one hundred or more patients and in which the percentage achieving one or more years completely seizure-free was clearly stated have been included. Interpretation of the results is often difficult because most have been retrospective surveys and the basis upon which patients were selected is often not clearly stated.

Currie et al (1971) retrospectively identified 666 cases of temporal lobe epilepsy who had attended an adult neurology outpatients department between 1949 and 1967. The mean duration of epilepsy at entry into the study was six years and patients were followed for a mean of seven years. Forty per cent of patients achieved a one year period completely free of all seizures, results which are in broad agreement with the conclusions of Rodin. A more recent study, however, suggested a far better prognosis. Schmidt et al (1983) described the clinical course and the long term prognosis in a 155 patients with complex partial seizures who were followed for a mean of ten years. Ninety-six (62%) had complete control of seizures, including auras, for a minimum of two years. Patients with tumours and previous

TABLE 1:12 RECENT STUDIES OF THE PROGNOSIS FOR SEIZURE CONTROL IN EPILEPSY

Author	Number of Patients	Duration of Remission, (years)	Percentage in Remission
Currie et al,1971 *	666	1	40
Janz, 1972	533	1	44
Ohtahara et al,1977 +	431	3	76
Okuma & Kumashiro, 1981	1838	3	58
Sofijanov, 1982 +	512	2	50
Schmidt et al, 1983 *	155	2	62

* Temporal lobe epilepsy
+ Childhood epilepsy

neurosurgical interventions were excluded. They all attended the private practice of one of the authors, but the selection criteria were not stated.

Janz (1972), in a retrospective study, identified 900 patients with epilepsy who attended his clinic during three one year periods in 1953, 1957 and 1961. One hundred and seventy two patients who were lost to follow up, 86 had died and 95 cases of "acute epilepsy" were excluded. The remaining 533 cases with chronic epilepsy were studied. Chronic epilepsy was defined as a minimum duration of illness of two years and at least six major attacks during this time. The duration of follow up was not stated. Forty four per cent were found to have been seizure free for one year or more.

Two of the studies have been confined to childhood epilepsy. Ohtahara et al (1977) studied 431 patients seen in a paediatric outpatient department, all of whom had experienced two or more seizures in the three years prior to first assessment. Seventy four per cent were aged 6 years or less. The analysis of prognosis appears to have been retrospective. After a total follow up period of at least 5 years 327 (76%) had complete control of seizures for three or more years. It appears however that an unstated number of patients with "minor" seizures were controlled for only six months, perhaps explaining the high remission rates found in this study. Sofijanov (1982) studied 512 children who had experienced at

least two afebrile convulsions separated by a minimum of 24 hours. The methods of case selection, which were presumably retrospective, were not given. Patients were followed for between four and ten years and actuarial statistical analysis was used. Seven years after the diagnosis the probability of being in two year remission was fifty percent.

The most extensive work published has been the report of the Japanese Multi-institutional Study (Okuma & Kumashiro, 1981), which was based on 1838 patients. Unlike the studies described above the methods of case selection were carefully defined. Initially three groups of patients who attended ten years, five years, and three years prior to the onset of the study were obtained. Amongst these, only those patients in whom the onset of seizures had been within five years of the first visit were selected. In this manner all patients entered had a duration of epilepsy not exceeding five years. An unstated number of patients with single seizures and an abnormal EEG were included. Unfortunately, 58% were lost to follow up and the mean duration of follow up was not given. In 58% seizures were controlled for three or more years.

e. Community Surveys of Prognosis in Epilepsy

Four community surveys of prognosis in epilepsy, based on an unselected sample of the population, have been undertaken. All of them were retrospective, in some instances relying on

the identification of cases diagnosed many decades previously. Details of clinical characteristics have in general been scanty.

Annegers et al (1979) used the record linkage system of the Mayo Clinic to identify all cases of epilepsy diagnosed in Rochester, Minnesota between 1935 and 1974. Epilepsy was defined as two or more seizures and those in whom an acute provoking cause could be established were excluded. From a total of 618 cases identified, 93 died and in a further 68 follow up or documentation was inadequate. Of the remaining 457 patients, 328 were followed for at least ten years and 141 for at least twenty years. Actuarial statistics were used to analyse the percentage of patients in remission. Ten years after the diagnosis the probabality of being in five year remission was 61% and at twenty years was 70%. Twenty years after the diagnosis 50% of patients were in remission and off medication. The authors considered three possible reasons for the good prognosis. Although prolonged follow up may have contributed this was not considered important as most remission occurred early in the course of the illness. As the study was community based a wide variety of patients with epilepsy were included. The most important factor, however, was felt to be identification of patients from the onset of the disorder.

Closely similar results were obtained by Goodrige & Shorvon (1983). One hundred and twenty two patients were retrospectively identified from general practioner records. It appears that in the analysis of prognosis 22 patients with single seizures and an unspecified number with seizures occurring in the context of an acute cerebral disturbance such as head injury or alcohol withdrawal were included. Regardless of medication status the probability of being in two year remission 15 years after the diagnosis was sixty eight per cent.

The study of Sillanpaa (1983) was conducted in South West Finland and was confined to children. Only patients who had undergone hospital treatment were included. Epilepsy was defined as at least three seizures occurring at intervals of at least one week. An unspecified number was seen by the author and follow up data was obtained by contact through the post. After a mean follow up of 21 years 66% had been seizure free for one year or more. Another community based survey in children has recently been reported from Sweden (Brorson & Wrane, 1987). Two thirds of cases were identified retrospectively and patients were followed for periods of up to 12 years. Fifty-six percent experienced a remission of at least 3 years. In a further series of 68 patients who were identified on the basis of incidence rates and followed prospectively the outcome was better with 78% achieving remission. Seizures were classified into focal, petit mal,

minor motor, grand mal and "others" but the proportion with each seizure type and any effect on prognosis was not commented upon.

f. Prognosis in Childhood Epilepsies

Amongst the childhood epilepsies there are a number of syndromes in which the prognosis has been studied in some detail. The classification and clinical features of these syndromes have been given in a previous section (see page 25) and the outcome of the most important of these will be briefly considered here.

i. West Syndrome

There is general agreement that the prognosis in children with West Syndrome is poor. The studies that have examined this group of patients are summarised in Table 1:13. Only those in which the prognosis for both seizure control and neurological development was given, and which were based on 100 or more patients have been included. The overall case fatality is of the order of 20%. Infantile spasms invariably disappear by the age of 5, whether or not treatment has been given (Jeavons, 1985). As many as 50% develop chronic seizure disorders, including Lennox-Gastaut Syndrome. The outlook in terms of cognitive and physical disability is particularly poor with as many as four-fifths mentally retarded, many of

TABLE 1:13 PROGNOSIS IN WEST SYNDROME

Authors	No of Cases	Follow-up years	Died %	Continuing Seizures % *	Normal IQ % *	Cerebral Palsy % *
Jeavons et al, 1973	150	2-12	22	48	16	37
Kurukawa et al, 1980	205	>5	-	43	15	-
Matsumoto et al, 1981	194	6	16	56	19	46
Riikonen, 1982	214	10	20	60	12	-
Bellman, 1983	267	1	6	26	28	29
Cavazutti et al, 1984	183	5-10	8	30	18	33

Percentages refer to those surviving
- not stated

them severely so, and about one-third having physical handicaps, usually cerebral palsy. The outcome is worst amongst patients in whom the illness develops before the age of four months and those with symptomatic seizures and developmental delay prior to the onset of seizures (Bellman, 1983).

ii. Lennox-Gastaut Syndrome

The prognosis is also poor in Lennox-Gastaut Syndrome and the disease is said to become chronic in the majority of cases, although in idiopathic cases the outlook may be better (Beaumanoir, 1985,b). A complete seizure free recovery has been reported to occur in only 7% of cases (Gastaut et al, 1973). In Oller Daurella's series (1973) only one patient became seizure free and had a normal EEG. The outlook is particularly poor in those patients with symptomatic seizures, cases which are preceded by West Syndrome and those with onset before the age of 3 (Baumanoir, 1985,b). The presence of severe slowing of background rhythms on the EEG is also associated with a poor outcome but the proportion of the EEG which is occupied by slow spike and wave is not of prognostic value (Blume et al, 1973). In general very few prognostic studies have been undertaken in Lennox-Gastaut Syndrome, possibly because of continuing uncertainty about its nosological position. A number of authors have included small numbers of patients, of the order of 40 to 60, amongst

unselected series of patients with childhood epilepsy (Sofijanov, 1982; Okuma & Kumashiro, 1981). In none of them were diagnostic criteria given. All have reported higher remission rates, of the order of 40% suggesting that the series of Gastaut et al (1973) and Oller Daurella et al (1973) may have included a disproportionate number of chronic intractable cases. Kurokawa et al (1980) found that 42 out of 123 cases of Lennox-Gastaut who were followed for at least five years became seizure-free.

iii. Childhood Abscence Epilepsy (Petit Mal, Pynknolepsy)

The first description of petit mal in the English speaking literature appears to have been that of Aidie (1924) who noted the tendancy of the condition to undergo spontaneous remission.

> "In ordinary epilepsy spontaneous recovery does not occur in more than 2% or 3% of cases (Kraepelin); a spontaneous termination of the disease is an event too rare to be reasonably anticipated in any given case (Gowers); in the cases of Pyknolepsy that conform to the strict requirements that I shall lay down later, spontaneous termination is a rule to which I have been unable to find a single exception."
>
> Aidie (1924)

Although it has generally been assumed that petit mal has a good prognosis the published literature on the subject is, in fact, highly contradictory. The prognostic studies are summarised in table 1:14. The remission rates refer to

TABLE 1:14 PROGNOSIS IN CHILDHOOD ABSCENCE EPILEPSY. THE PERCENTAGE OF PATIENTS WITH COMPLETE CONTROL OF ABSENCE SEIZURES FOR AT LEAST ONE YEAR

Author	Number of Patients	Follow-up (years)	Percent Seizure Free
Hollowach et al, 1962	88	1-12	37
Hertoft, 1963	50	8	48
Currier et al, 1963	32	18	37
Livingston et al, 1965	117	5	79
Gordon, 1965	70	2-6	51
Gibberd, 1966	139	NS	42
Dalby, 1969	161	5	79
Loiseau et al, 1983	90	16	63
Gastaut et al, 1986	26	30-37	19

control of abscence seizures alone. As can be seen the prognosis has been reported to be favourable in a widely differing proportion of cases.

A number of authors have included cases who in all likelihood did not suffer from petit mal. In the study by Hollowach et al (1962) 24% of the patients had associated neurological handicaps and only 35% had 3 per second spike and wave on the initial EEG. It is likely that a considerable proportion of the patients suffered from partial epilepsy. In only two studies (Currier et al, 1963; Loiseau et al, 1983) were patients with neurological deficits clearly excluded and in only half of the remaining studies did all the patients meet the diagnostic criteria relating to EEG abnormalities Hertoft, 1963; Livingston et al, 1965; Dalby, 1969). Loiseau el al (1983) reported that 63% of patients had been free of absence attacks for two or more years after a mean follow up of 16 years. However, a quarter of the patients also had myoclonic seizures, and if these patients were excluded, the overall prognosis was considerably better. Similarly, Gibberd (1966) reported that 18 patients in his series had "frequent myoclonias" although similar information concerning other seizure types was not supplied by any of the other authors.

The five studies which reported a poor prognosis (Hertoft, 1963; Currier et al, 1963; Gordon, 1965; Gibberd, 1966; Gastaut et al, 1986) were based on patients attending adult

neurology clinics or EEG departments. This method of selection will, of course, lead to a strong bias in favour of those patients in whom seizures persist into adulthood. In all of these studies virtually all the patients were aged 15 or over at the time of inclusion into the follow-up period.

A factor that complicates prognosis in petit mal epilepsy is the development of tonic clonic seizures. Tonic clonic seizures are said to occur in about one third to one half of patients (see Table 1:15). The higher figures reported by Gibberd (1966) and Gastaut et al (1986) are almost certainly due to patient selection. There is good agreement that in the majority of cases tonic clonic seizures occur for the first time between the ages of 10 and 15 years, usually about five years after the onset of absence attacks. Occasional cases have been reported where tonic clonic seizures developed after the age of 20 years (Gibberd, 1966). All authors are in agreement that a later age of onset of abscence attacks (over the age of 10 years) is associated with a higher risk of developing tonic clonic seizures.

Few studies have either had a long enough duration of follow up or adequate documentation of outcome to assess the prognosis for control of tonic clonic seizures. Currier et al (1963), Gordon (1965) and Loiseau et al (1983) stated that seizures ceased in about one half of patients. All authors have said that the attacks can usually be easily controlled on medication, or occur at very infrequent intervals (Gibberd, 1966; Gastaut et al, 1986).

TABLE 1:15 PROGNOSIS IN CHILDHOOD ABSENCE EPILEPSY. THE PERCENTAGE OF PATIENTS DEVELOPING TONIC CLONIC SEIZURES

Author	Total number of patients	Patients with tonic clonic seizures N (%)
Hollowach et al, 1962	72	24(33)
Hertoft, 1963	50	19(38)
Currier et al, 1963	32	12(38)
Livingston et al, 1965	117	54(46)
Gordon, 1965	70	25(36)
Gibberd, 1966	139	82(59)
Dalby, 1969	161	74(46)
Loiseau et al, 1983	90	(36) *
Gastaut et al, 1986	26	24(92)

* Actuarial Percentage

iv. Benign Partial Epilepsies of Childhood

There is complete agreement in the literature on the uniformly good prognosis in Rolandic Epilepsy. Most of the early series were based on patients identified by EEG features alone. Gibbs & Gibbs (1959-1960) studied 739 patients who had mid-temporal spikes on their EEG. In contrast to those who had anterior temporal spikes, who tended to have psycomotor seizures and a poorer prognosis, in these patients it was found that the EEG abnormalities rarely persisted beyond the age of 15 years. Smith & Kellaway (1964) found that in 200 children with centro-temporal spike discharges the abnormality rarely persisted for more than 4 years. Longitudinal studies of children with Rolandic spikes but no seizures (Cavazutti et al, 1980) suggest that there is a strong tendency for the abnormality to disappear spontaneously.

The most carefully documented study has been that of Blom et al (1972). Forty cases were followed between 11 and 16 years. Thirty-eight were seizure free for periods ranging from 4 to 13 years and 28 had discontinued medication. One patient had a recurrence of seizures related to poor compliance with medication and another had an isolated attack 3 years after stopping treatment. In a subsequent study based on the analysis of the same patients 10 years later (Blom & Heijbel, 1982) only one patient was still on medication and one had

developed seizures related to alcohol abuse. A more recent study (Loiseau et al, 1983) has confirmed a uniformly good prognosis. In benign partial epilepsy with occipital paroxysms complete seizure control is said to occur in 60% of cases (Gastaut, 1985).

3 PROGNOSIS FOLLOWING ANTICONVULSANT WITHDRAWAL

a. Seizure Recurrence

The most important published studies that have examined prognosis following anticonvulsant withdrawal are summarised in table 1:16. It would appear that the relapse rate is not inconsiderable, and has been reported to occur in 20% to 40% of patients on stopping medication. Most recurrences happen during or shortly after the actual period of drug withdrawal. Juul-Jensen (1968) found that amongst 79 patients experiencing a recurrence, 35 did so during drug reduction and a further 23 by one year of follow-up. Similarly Todt (1984) reported that 86% of all recurrences had taken place within one year after drug reduction. In the study by Thurston et al (1982) patients were followed for prolonged periods of time, ranging from 13 to 23 years. From a total of 41 patients who relapsed, 22 (53%) did so by one year and 33 (80%) by five years. Late relapses were seen only rarely.

There appears to be little risk of precipitating uncontrollable epilepsy following drug withdrawal in patients who have been seizure free for at least two years. Juul-Jensen (1968) found that all patients who relapsed responded immediately to reinstitution of therapy. Todt (1984) reported that in 157 children who relapsed, 143 were placed back on medication immediately and of these 123

TABLE 1:16 STUDIES OF ANTICONVULSANT WITHDRAWAL. PERCENTAGE OF PATIENTS EXPERIENCING A SEIZURE RECURRENCE FOLLOWING DRUG REDUCTION

Author	No of Patients	Remission (years)	Rate of drug withdrawal (months)	Follow-up (years)	Relapse Rates (%)
Zenker et al, 1957 *	117	0.5	NS	NS	21
Juul-Jensen, 1968	196	2	2-3	5	40
Groh, 1975 *	375	3	6-48	5	20
Janz & Sommer-Burkhardt, 1976	253	2	NS	0.5-21	49
Oller-Daurella et al, 1976	138	5	NS	0.1-22	21
Van Heycop Ten Ham, 1980	150	3	NS	2	32
Emerson et al, 1981 *	68	4	2-3	0.5-6	26
Thurston et al, 1982 *	148	4	9	15-23	28
Todt, 1984 *	433	1	1-12	1-12	36
Shinnar et al, 1985 *	88	2	2-3	0.5-5	25
Bouma et al, 1987 *	116	2	1-2	4.3	20

* childhood epilepsy

subsequently had no further seizures. In 30 patients, the outcome was "problematic" but only one, an adolescent female with tonic clonic seizures, developed intractable epilepsy. Interestingly, Todt (1984) found that in the fourteen patients who remained off medication despite a relapse none had further seizures.

Six of the studies shown in table 1:16 were based on a paediatric population, probably reflecting the greater willingness to withdraw drugs in children who have been seizure-free for prolonged periods. All of the studies were hospital based. Shorvon (1984) has argued that this will lead to an unduly gloomy view when compared with epilepsy in the community. Although this criticism is in general correct, studies of anticonvulsant withdrawal will obviously select only those milder cases which are in remission. In the study by Todt (1984) for example 78% of cases had a duration of epilepsy of less than two years, a result similar to the community survey of Goodridge & Shorvon (1983) where patients were selected from general practice records. None of the studies have included a control group on treatment. There is little information in the literature on the relapse rates amongst patients in prolonged remission who are maintained on treatment. Annegers et al (1979) found that the probability of relapse for patients who had experienced a five year remission was 24% by ten years.These results are similar to those of Thurston et al (1982) following planned anticonvulsant withdrawal.

b. Prognostic Factors

There is good agreement that a long duration of active epilepsy or a large total number of seizures prior to control is associated with a higher recurrence rate following drug withdrawal. Similarly, patients with associated neurological handicap and those with partial seizures have been reported to have a worse prognosis, although there is not complete agreement on the latter (Janz & Sommer-Burkhardt, 1976). These factors are in good agreement with those identified by Rodin (1968) as being associated with a poor prognosis for seizure control in patients with chronic epilepsy.

Opinions have differed concerning the importance of the EEG in predicting seizure recurrence. In the study by Juul-Jensen (1968) only half the patients had this investigation performed immediately prior to drug withdrawal. A small number of patients, seven in all, with delta foci, focal spikes or bilateral paroxysmal changes had a significantly higher recurrence rate. Thurston et al (1982) and Janz & Sommer-Burkhardt (1976) found that the EEG was of little prognostic significance. Shinnar et al (1985), in childhood epilepsy, reported that the relapse rate was double amongst those with an abnormal EEG compared to those in whom it was normal. The presence of specific electroencephalographic features such as spikes or slow wave abnormalities were of greater use in predicting outcome. Todt (1984) found that

children with paroxysmal changes on the EEG were particularly likely to relapse. This author also emphasised the importance of an improvement in consecutive recordings in determining a good prognosis following drug withdrawal.

Similarly little agreement exists concerning the importance of age of onset of epilepsy in determining the prognosis following anticonvulsant withdrawal. Two of the studies shown in table 1:16 which found a high recurrence rate (Juul-Jensen, 1968; Janz & Sommer-Burkhardt, 1976) were conducted in adults. Both of these, however, used a shorter period of remission prior to drug withdrawal than most of the other studies. Although prognosis is known to be particularly good in petit mal and the benign partial epilepsies of childhood, anticonvulsant withdrawal studies have in general only included small numbers of children with these disorders. Two studies that compared relapse rates by specific age groups found no significant difference between them (Todt, 1984; Thurston et al, 1982). Juul-Jensen (1968) reported a higher recurrence rate in the age group 0 to 9 whilst Janz & Sommer- Burkhardt (1976) and Shinnar et al (1985) found that the median age of those who relapsed was higher than those who remained seizure free.

An area of particular importance is the influence of duration of remission and the rate of anticonvulsant withdrawal in determining relapse rates. These are important practical

issues in patient management yet they appear to have received only scant attention. It is the usual clinical practice in this country to consider anticonvulsant withdrawal in patients in whom all seizures have been suppressed for a minimum period of two years. The drugs are usually withdrawn over a period of two to three months. This was the criterion used by Juul-Jensen (1968) and this paper has probably been important in determining current practice. Juul-Jensen (1968) stated that duration of remission had no influence upon recurrence following anticonvulsant withdrawal. Few details, however, concerning this important aspect of management were given, and no randonmization procedure was used. Other studies, particularly those from North America (Emerson et al, 1981; Thurston et al, 1982; Oller-Daurella et al 1976), have used longer remission periods of 4 to 5 years, and all of these have reported lower recurrence rates of the order of 20%. Similarly, both Thurston et al (1982) and Oller-Daurella et al (1976) used a much slower rate of anticonvulsant withdrawal. In the former the drugs were reduced over a period of 9 months and this was done sequentially in those who were on polytherapy.

Groh(1975) reported that the proportion of patients relapsing following drug withdrawal was inversely related to the previous period of remission. This study was based on a retrospective analysis which may bias the results as treatment may have been continued in those patients in whom

relapse was thought to be less likely to occur. Todt (1984), however, used randomisation to determine both the seizure free interval prior to withdrawal and the rate at which the drugs were reduced. The results have been reproduced in table 1:13. There is a very clear direct relationship between slower anticonvulsant withdrawal and an increasing period of terminal remission with a subsequent lower relapse rate. If these findings are confirmed a more cautious approach to anticonvulsant withdrawal may be appropriate.

TABLE 1:17 THE INFLUENCE OF DURATION OF REMISSSION OF SEIZURES AND RATE OF DRUG REDUCTION ON THE RELAPSE RATES FOLLOWING ANTICONVULSANT WITHDRAWAL. (adapted from Todt, 1984)

Seizure Free Period (years)	Total Number of Patients	No. of Patients with Relapse N(%)
1	59	33(56)
2	137	69(50)
3	104	26(25)
4	133	29(22)
Length of Reduction Period (months)		
1	41	29(71)
3	144	82(57)
6	114	25(22)
12	134	21(16)

CHAPTER TWO

THE PRESENT INVESTIGATION

A. INTRODUCTION

In the previous chapter a general review of the literature relating to the prognosis of patients with epilepsy was presented. Before considering the specific topics which form the experimental basis of this thesis a number of general observations should be emphasised. Firstly, and most importantly, virtually all the studies that have examined prognosis have been based on the observations of patients with chronic long standing epilepsy. The natural history of the disorder in this group of patients has been studied in considerable detail. The most important work in this area has been undertaken by Rodin (1968) who in addition to describing the general prognosis of epilepsy has identified a number of factors that are of importance in predicting prognosis in chronic epilepsy.

In marked contrast, the prognosis of epilepsy during the early years of treatment has been virtually ignored in the literature. Only one author appears to have commented upon the initial response to treatment and this was in relation to the law concerning driving licences (Kuhl et al, 1967). There has been no previous study of the patterns of seizure

recurrence at the onset of the disorder in either treated or untreated epilepsy. Nor has the implication that this may have for subsequent prognosis been examined. Although a number of authors have studied the outcome in patients presenting with a single seizure, the results have been widely conflicting and at variance with data obtained from the epidemiology of epilepsy (see tables 1:7 & 1:8).

A number of other inadequacies are to be found in the literature that have led to difficulty in the interpretation of the results of prognostic studies. Some authors have included patients with seizures occurring in the context of acute metabolic or neurological disturbances (Blom et al, 1978; Hirtz et al 1984;, Goodridge & Shorvon, 1983). Others have excluded from the definition of epilepsy patients with symptomatic seizures or those with evidence of structural brain disease (Strobos, 1959). The definition of epilepsy has varied from three or more seizures occurring at intervals of one week (Sillanpaa, 1983) to a minimum duration of two years with at least six major attacks occurring during this period (Janz, 1972) whilst others have included patients with a single seizure and an abnormal EEG (Okuma & Kumashiro, 1981). The literature abounds with such inprecise terms as "minor" seizures (Ohtahara et al, 1977), "fainting spells" (Trolle, 1960) or "acute epilepsy" (Janz, 1972). In analysing prognostic factors, some authors have based classifications upon the EEG alone (Gibbs & Gibbs, 1959-1960; Smith &

Kellaway, 1964; Strobos, 1959) , with little reference to associated clinical features, whilst others have introduced novel classifications to suit the purposes of the particular study (Annegers et al, 1979; Brorson & Wranne, 1987). The problems of heterogenicity and varying definition have been particularly prominent amongst prognostic studies in childhood epilepsy. Many of the prognostic studies that have been undertaken both in adults and children have been retrospective surveys. The outcome has been couched in such inprecise terms as "improved" or "reduction in seizure frequency". Not only is it very difficult to reach clear conclusions concerning prognosis on the basis of such statements but it is virtually impossible to subject them to any meaningful form of statistical analysis. Most prognostic studies have analysed outcome in terms of crude remission or relapse rates, rather than using life table calculations.

Treatment has, in general, received only scant attention in prognostic studies. The tendency to include patients who were treated following a first attack amongst those who suffered from epilepsy has given rise to controversy in historical literature. Similarly current practice concerning the initiation of treatment appears to differ widely (see table 1:10), which itself is largely due to the lack of clear data on the early prognosis of epilepsy. Many studies that have examined the outcome make either no mention of treatment or at most give a list of drugs that were used. The

continuing use of polypharmacy and other unsatisfactory aspects of treatment makes interpretation of results difficult. There have been no previous prognostic studies that included anticonvulsant level monitoring to assess either optimal use of drugs or poor compliance with medication. It is very difficult on the basis of the current literature to assess the impact that the currently available drugs have had on the prognosis of epilepsy. It is even harder to determine secular trends that could be attributed to advances in drug development or to determine differences in efficacy of the currently available compounds.

B. THE EARLY PROGNOSIS OF EPILEPSY

The patients who formed the basis of the experimental work in this thesis were all consecutive new referrals to an adult neurology outpatients department with previously untreated epilepsy. All the patients seen were considered for inclusion into trials of monotherapy conducted by Dr. E. H. Reynolds at Kings College Hospital, London. The author's interest in the early prognosis of epilepsy developed during the recruitment, assessment, randomisation and subsequent follow-up of patients entered into these trials. An analysis of the prognosis in these patients provided a unique oppertunity to study the natural history of epilepsy at the onset of the disorder in a hospital based population.

Three aspects of the early prognosis of epilepsy have been studied:

1) The prognosis for seizure control in a series of 106 patients with newly diagnosed epilepsy who were followed prospectively for periods of up to eight years.

2) The prognosis following a first seizure in a series of 214 patients who were consecutively referred to the department with recent onset of one or more tonic clonic seizures.

3) An analysis of the intervals between seizures in a further series of 183 patients with two or more untreated tonic clonic seizures.

It will become apparent from the work considered here that the patterns of patient referral, the selection criteria used and the timing of the initiation of anticonvulsant medication may all have a crucial impact on the results of prognostic studies in epilepsy. Although each of the chapters considers a specific aspect of the early prognosis of epilepsy the patients that form the bases for each study were drawn from the same source. A general description of the patients and methods which are common to the three studies will be given below. The appropriate modifications that were needed to suit the particular aspect of the early prognosis of epilepsy under study will be given at the start of each chapter. Each chapter is followed by a discussion which broadly covers the interpretation of the results and a comparison with the results of previous prognostic studies.

In the final chapter the most important conclusions will be emphasised and the broader issues that have arisen from all three studies will be discussed.

C PATIENTS AND METHODS

1. Trials of Monotherapy in Newly Diagnosed Epilepsy

Reynolds et al (1976) initially reported the outcome in 31 adult outpatients who were treated with phenytoin alone with the aid of anticonvulsant level monitoring. The initial studies were subsequently extended to include patients taking carbamazapine (Shorvon et al. 1978). The response to single drug therapy was analysed in a series of 94 patients after a median interval of 32 months (Shorvon & Reynolds, 1981). Twenty four patients had their seizure controlled with suboptimal levels of either phenytoin or carbamazepine and 22 patients with optimum anticonvulsant levels. Twenty six patients experienced seizures initially but were subsequently controlled when the dosage was increased and optimum anticonvulsant levels were achieved. Six patients failed to achieve optimum anticonvulsant levels and 16 patients (17% of the total) failed on monotherapy.

On the basis of the results of this pilot study an MRC trial was initiated and patient recruitment was started in 1981. Both adults and children were included. The latter were

patients attending the paediatric department at Kings College Hospital, and at Guys Hospital under the care of Dr. B. Neville. Subsequently adult patients were recruited from Walton Hospital, Liverpool under the direction of Dr D. Chadwick. The patients studied in this thesis were adults and children under the care of the neurology outpatients department at Kings College Hospital. In contrast to the pilot study patients were stratified on the basis of seizure type and associated neuropsychiatric handicaps. They were randomised to treatment with either phenobarbitone, phenytoin, sodium valproate or carbamazapine. The use of phenobarbitone in children was subsequently abandoned because of a high incidence of side effects, particularly behaviour disorders (MacArdle et al, 1987). In patients who failed to respond to monotherapy the potential for adding a second drug was assessed. Patients were followed prospectively in a special clinic established for this purpose. These studies, which are currently in progress, will be analysed to assess the comparative efficacy and toxicity of the established anti- convulsant drugs given as monotherapy in adults and children. Particular emphasis has been placed on the comparative effects of the drugs on cognitive function. Prior to treatment and at regular follow up intervals a batch of specifically designed psychometric assessments were undertaken (Andrewes et al, 1986).

The initial pilot study represented a unique group of patients who had been identified and followed as a cohort prospectively from the onset of the illness for the period of almost a decade. Detailed documentation of the numbers, types and timing of seizures whilst on treatment were undertaken. Because of this they provided an opportunity to examine the early prognosis of epilepsy on the basis of carefully gathered prospective data. Furthermore, unlike all other prognostic studies a consistent policy treatment with extensive use of anticonvulsant level monitoring was used throughout follow up. The outcome of the patients entered into the pilot trial is given in Chapter 3. Patients who were considered for entry into the subsequent MRC trial formed the basis of the analysis of the patterns of seizure recurrence at the onset of epilepsy that is given in chapters 4 and 5.

2. Referral of Patients

The patients who were entered into the monotherapy trials described above all had newly diagnosed previously untreated epilepsy and were referred under the care of the adult neurology clinic at Kings College Hospital. Kings College Hospital is a District General Hospital in South-East London serving an urban population. The patients were referred directly by general practitioners or casualty offficers in about equal numbers. The studies were carried out with the cooperation of the other consultant neurologists in the

department and all the patients sent to the hospital were referred under the care of Dr E. H. Reynolds to assess their suitability for inclusion. Following the initial referral letter a period of about 4 weeks usually elapsed before they were seen in the neurology outpatients department. Although every effort was made to see patients as soon as possible this period corresponded to the time spent on the general neurology outpatients waiting list. If it was felt that patients required anticonvulsant medication initial investigations were undertaken and patients were started on treatment after a period of about 3 to 4 weeks.

The referral patterns described above are likely to be broadly similar to those encountered by other consultant neurologists in this country, the majority of whom see patients referred to district general hospitals by general practitioners or casualty officers. Although the department at Kings College Hospital had a specific interest in the treatment of epilepsy the patients seen were likely to be representative of those seen in contemporary neurological practice. Available evidence suggests that the majority of patients in the community who develop seizures de novo are referred to a neurology department for assessment, appropriate investigation and advice concerning initiation of treatment (Hopkins & Scrambler, 1977; Godridge & Shorvon, 1983).

All patients entered into the trials were consecutive new referrals with previously untreated seizures. Cross-sectional selection was avoided in that patients already attending the department for treatment of epilepsy were not considered. Some patients, although presenting with recent onset of seizures, gave a history of one or more attacks, often occurring many years previously. These were considered for inclusion only if they had never received anticonvulsant medication at any time.

3. Patients Excluded

The following groups were excluded from the study:

a. Those with a progressive neurological disorder such as brain tumour which was apparent at the time of diagnosis. A number of patients developed tumours during the course of follow-up and these have been included in the analysis of prognosis.

b. Seizures occurring in the context of acute metabolic disturbance such as hypoglycaemia, uraemia or liver failure.

c. Seizures occurring in the context of an acute neurological disorder such as meningitis, stroke or immediately following head injury.

d. Seizures precipitated by drugs or ocurring in the context of alcohol dependence.

e. Febrile convulsions. Patients who gave a past history of febrile convulsions and subsequently presented with a history of apparently unprovoked seizures were included.

4. Assessment of Patients

At the time of first assessment in the neurology outpatients department a full history and a general and neurological examination was undertaken in the usual manner. In each case particular attention was paid to obtaining a full witnessed history of the seizures that had occurred. The dates of individual seizures were obtained from the patient and these were supplemented by information obtained from the referring general practitioner or casualty officer. In many instances the date of the first and often subsequent attacks had been recorded by the referring doctor.

In patients who entered the pilot study and the MRC trial the following investigations were undertaken in all cases. -Haematology: a full blood count was performed in the haematology laboratory at Kings College Hospital. Serum Vitamin B12 levels and serum and red cell folate estimations were carried out at Northwick Park Hospital in the laboratory of Dr I. Chanarin.

-Biochemical Screen: an automated analysis of urea and electrolytes, random blood glucose, calcium, phosphate and serum proteins and liver enzymes was carried out in the hospital laboratory.

-Syphylis serology: a routine screen of VDRL and TPHA was carried out. As the catchment area contained a high proportion of patients of Afro-Caribbean origin a number showed false positives due to cross reaction with yaws. These patients were admitted to hospital for CSF examination to exclude active syphilis.

-Pre treatment EEG. These were done by the tecnical staff in the neurophysiology departments at the Maudsley and Kings College Hospitals. Routine 16 channel records were obtained in the resting state and following hyperventilation and photic stimulation. The records of patients entering the MRC trial were reported upon by the author.

CT brain scans were carried out on the majority of patients entering the pilot study and all those in the MRC trial. Pretreatment psychometric assessment, which included performance, verbal and full scale IQ and a further battery of tests to examine the effects of anticonvulsant drugs on cognitive function were performed on all patients entering the MRC trial.

5. Data Collection and Definitions

The clinical data relating to each of the patients was recorded on a proforma which has been reproduced in Appendix 1. The following definitions were used.

i. Age of Onset: The age at the time of the first afebrile seizure.

ii. Classification of Seizures: Seizures were classified on clinical grounds in accordance wtih the revised version proposed by the Commission on Classification and Terminology of the International League against Epilepsy (1981). Tonic clonic seizures were diagnosed on the basis of sudden loss of consciousness with convulsive movements of the limbs, tongue biting and incontinence. They were classified as partial seizures secondarily generalised if there was evidence of a significant aura or post ictal localising signs such as Todds paralysis. Partial seizures were diagnosed on clinical grounds and designated complex or simple using the criteria of the international classification. Petit mal was diagnosed on the basis of a characteristic history of absence seizures occurring in childhood in association with three per second spike and wave seen on the EEG.

iii Symptomatic Epilepsy: Epilepsy was considered symptomatic if there was evidence from the past history or examination,

or evidence on C.T. scan, of a cerebral lesion likely to cause seizures. Post traumatic epilepsy was diagnosed on the basis of a past history of a significant head injury associated with skull fracture or a prolonged period of unconciousness greater than 24 hours (Caveness et al, 1979). Epilepsy related to CNS infection was diagnosed if there was a clear history of previous bacterial meningitis or viral encephalitis.

iv. Family History: Epilepsy in first degree or second degree relatives was defined as the occurrence of two or more afebrile seizures, regardless of causation.

v. Associated Handicaps: A neurological handicap was defined as the presence of significant neurological deficit such as a hemiparesis or the presence of cognitive impairment with a full scale IQ of below 85. A pyschiatric handicap was defined as previous psychiatric illness or a similar disorder arising during treatment of epilepsy which was of sufficient severity to justify referral to a psychiatrist. A social handicap was said to occur if social difficulties arose that were of sufficient severity to justify referral to a social worker.

vi. EEG Features: The abnormalities on the pretreatment EEG were classified following review of the records. The abnormalities on the EEGs for patients entered into the pilot

study were listed as follows: the presence or absence of epilepiform abnormalities; the presence or abscence of slow wave changes which were subdivided into focal or generalised and were graded in severity as +,++ or +++. In patients entering the MRC trial the records were graded into abnormal or normal. Abnormal records were further subdivided into those with slow wave or epileptiform abnormalities, either focal or generalised.

6. Treatment and Follow up

It was the general treatment policy throughout the period of pilot study and the MRC trial to initiate medication only after the occurrence of two or more seizures. In view of the lack of clear guidance in the literature decisions were often made on the basis of individual clinical assessment. In a patient who had experienced two apparently unprovoked seizures during the space of one year there was general agreement that treatment was needed. If however only a single seizure had occurred, the intervals between attacks exceeded one year or some of them were related to acute precipitating events such as lack of sleep then treatment was often witheld and the patient kept under observation. In a small number of patients, particularly children in whom the initial attack was a prolonged generalised convulsion, treatment was given following a single seizure. The decision to start treatment in patients with partial seizures was made

on the basis of clinical judgment alone. In the great majority of instances these patients had experienced a large number of attacks, often occurring over a prolonged period of time, and the decision to treat presented few problems. A number of patients with partial seizures, particularly if these were not associated with any disturbance of consciousness, declined treatment.

It was the treatment policy during the period of both pilot study and the MRC trial to use a low starting dose of drug which was then increased on the basis of clinical response. The total daily starting doses for phenobarbitone, phenytoin, sodium valproate and carbamazepine were 60 mg, 200 mg, 400 mg and 200 mg respectively. Each of the drugs were given as twice daily divided dosages. If seizures continued the dose of the drug was increased until an optimum anticonvulsant level was obtained. The increments in dosage for phenobarbitone, phenytoin, sodium valproate and carbamazepine were 30mg, 100mg, 200mg and 200mg respectively. If seizures were controlled on a suboptimum anticonvulsant level no further adjustment were made to the dosage. Patients who experienced two or more seizures despite an optimum level, in the abscence of evidence of poor compliance, were considered to have failed on monotherapy. In these patients the potential for addition of a second drug was considered.

Following the initial assessment in the general neurology

outpatients department patients were subsequently followed in a special epilepsy clinic. Patient were initially seen at intervals of two to three months. This policy was modified depending on clinical response. Some patients who presented difficulties in seizure control were seen at shorter intervals whilst those who entered prolonged remission were given six month follow-up appointments. Every effort was made to maintain complete follow up. Patients who failed to attend were written to personally and if no response was obtained from two letters information concerning outcome was obtained from their general practitioner.

7. Analysis and Statistics

As was noted previously there are a number of difficulties in developing appropriate statistical methods for analysing prognosis in epilepsy. Throughout this thesis widespread use has been made of actuarial statistics. The technique was initially developed to measure survival rates amongst groups of people with particular risk factors such as smoking or hypertension and is widely used in this manner by insurance companies. They gained particular importance in medical research in analysing outcome in trials of cancer treatment where the endpoint being measured was death of the patient (Peto et al, 1977). There first application to analysing prognosis in epilepsy was carried out by Alstrom (1950) who measured the actuarial percentage of patients achieving five

year remission by duation of follow-up. They were subsequently used by Annegers et al (1979) to analyse outcome in a community based study carried out in Rochester, Minnesota.

Actuarial analysis has two main advantages. The probability of the event occurring during each interval of follow up is related to the number at risk. This method, therefore, takes account of variable follow up using all available data. Secondly, the first occurrence of the event, for example, one year remission on treatment, is measured and the survival curve indicates the temporal relationship of remission to duration of follow up.

The method of derivation of the survival curve is simple. The total period of follow-up is divided into appropriate intervals, for example two or six months (Elwes et al, 1982). During each interval there are two possible outcomes. The patient may end or be lost to follow up, or the particular event that is being measured (the event of interest), for example death of the patient, may occur. One hundred patients may enter the study and during the first two month interval of follow up five will die and a further five will end follow up. The probability of dying during the first interval is 0.05. The probability of surviving is 1 - this measure, or 0.95. Ninety patients enter the next follow-up period, the so called number "at risk" for this interval.

Similar probabilities of survival are calculated for those those at risk for each succesive interval and are multiplied to give the cumulative probability of survival. This gives rise to the characteristic stepwise decrease of the survival curve. A further adjustment is needed as it is assumed that if patients end follow up during an interval it will, on average, occur in the middle of that interval. Using these principles a computer programme was written by the author to analyse some of the prognostic variables considered in the following chapters (see appendix 2).

The following prognostic parameters have been analysed using actuarial statistics: seizure recurrence following a first seizure; first seizure recurrence after starting treatment; first one and two year remission on treatment and first seizure recurrence after achieving remission. A number of general observations relating to the interpretation of survival curves should be empasised. It is of crucial importance that the number of patients at risk be clearly indicated on the figure. As was explained above this figure does not nessesarily correspond to the number of patients being followed up. When the number of patients at risk becomes small, it is unusual for the event of interest to occur. This leads to a prolonged flattening of the curve and a tendency for large variations and unreliable data at the end of follow up . Secondly it should be emphasised that

survival curves measure the cumulative probability of the occurrence of the first ever event of interest. For example each time a patient enters a first ever one year remission the curve rises and that patient is subsequently discounted from the analysis. The actuarial percentages given in the figures and quoted in the text refer to the cumulative probability of ever having been in remission, not those in remission at the particular point in time.

CHAPTER THREE

THE PROGNOSIS FOR SEIZURE CONTROL IN NEWLY DIAGNOSED EPILEPSY

A. INTRODUCTION

Virtually all the literature on the prognosis for seizure control in epilepsy has been based on the observation of patients with chronic epilepsy. In many of these patients, who accumulate in considerable numbers in specialised neurology or epilepsy clinics, the outlook for seizure control is poor. This has led many authors to emphasise the gloomier and less satisfactory aspects of prognosis in epilepsy (Rodin, 1968). In contrast the initial response to treatment and the prognosis during the early years of epilepsy have received only scant attention in the literature. In this Chapter an analysis of the outcome in 106 patients, who were followed prospectively from the onset of the disorder for periods of up to eight years, will be presented. The results will be presented with the following aims:

1. To analyse the prognosis for seizure control in newly diagnosed epilepsy

2. To assess the factors that are useful in

predicting prognosis at the onset of treatment

3. To assess the importance of the initial response to treatment in determining the subsequent prognosis in epilepsy

B. PATIENTS AND METHODS

The patients who form the basis of this study were all new referrals to the adult neurology clinic at Kings College Hospital seen over a five year period between 1974 and 1979. One hundred and six patients were identified and entered into a pilot study of monotherapy in newly diagnosed epilepsy. The details concerning the methods of patient selection, assessment data collection and treatment have been described in the previous chapter.

All patients were consecutive new referrals with previously untreated seizures. Cross-sectional selection was avoided in that patients already attending the Department for treatment of epilepsy were not considered. Each patient had experienced at least two tonic clonic seizures in the previous year and/or sufficient partial seizures to warrant treatment. The following groups of patients were excluded from the

study: patients with petit mal or myoclonic epilepsy; patients with progressive neurological disorders which were apparent at the time of first diagnosis; patients with seizures occurring in the context of fever or acute metabolic or neurological disorders.

A proforma was produced for each patient (see Appendix 1) recording the appropriate details concerning seizure history, past medical, social, psychiatric and drug history as well as the general and neurological examination and the results of initial investigations. The data for all 106 patients are shown in Appendix 3.

Following the initial assessment and investigations, treatment was started with phenytoin or carbamazepine on a non-randomised basis. The starting doses were 200 to 300 mg. for phenytoin and 200 to 600 mg. for carbamazepine, both in two divided doses. If seizures continued the dose was increased by 50 to 100 mg. increments for phenytoin and 100 to 200 mg. increments for carbamazepine until optimum anticonvulsant levels were obtained. If seizures were controlled on a sub-optimum level no further adjustment was made to the dosages. Optimum concentrations for phenytoin were 40 to 80 micromol/l and for carbamazepine were 16 to 32 micromol/l.

Patients were followed prospectively in a special epilepsy

clinic at intervals of two to three months although this varied depending on clinical need. For those patients who failed on treatment with monotherapy the policy was to add another drug and increase the dosage in an attempt to control seizures; if this occurred the initial drug was subsequently withdrawn.

In analysing seizure control all patients were included, regardless of medication status, up to the time of the last follow up. The occurrence of partial or tonic clonic seizures was noted at each clinic visit. If the timing of a seizure during the previous interval of follow up was uncertain it was assumed to have occurred in the middle of that interval. A preliminary analysis was undertaken by dividing the total follow-up period into six month intervals (Elwes et al, 1982). The prognosis for seizure control was assessed by measuring the actuarial percentage of patients achieving one and two year remission. On the basis of these initial results a more detailed study was done. The total follow up period from the time of starting medication was divided into two month intervals and the presence or absence of tonic clonic, partial or both seizure types for each two month interval period was recorded, see Appendix 4. The analysis of prognosis presented in this Chapter is based upon these data.

Kaplan - Meier Survival Curves were used to analyse the outcome (Kaplan & Meier, 1958). The following parameters were used: Time to first seizure, first one year remission and first two year remission and time to first seizure after periods of one, two, three and four years seizure free. The analysis was performed for partial seizures, tonic clonic seizures and all seizures combined. Factors of prognostic significance were assessed by comparing the actuarial percentages of patients achieving one year remission. The significant values of prognostic factors were assessed using the log-rank test (Peto et al, 1977).

C. RESULTS

1. Patient Characteristics

The characteristics of the patients entered into this study are shown in Table 3:1. Fifty-one patients (48%) were male and 55 (52%) were female. The median age at first seizure was 23, with a range of onset between 6 and 77 years. Fifty nine patients (55%) had experienced tonic clonic seizures alone prior to treatment, 22 (21%) had partial seizures alone and 25 (24%) patients had partial and secondarily generalised seizures. Eighty four patients experienced tonic clonic seizures. In assessing pre-treatment tonic clonic seizure frequency three patients who experienced only one seizure and two patients with poor documentation of the total number of attacks were excluded from the analysis. In the remaining 79 patients, 45 (57%) had a high pretreatment seizure frequency, defined as two or more seizures per month and 34 patients (43%) had a low seizure frequency.

Thirty five patients (33%) had symptomatic epilepsy. The commonest causes of epilepsy were cerebrovascular disease in 7 patients, post traumatic in 4, central nervous system infection (meningitis or encephalitis) in 5 and a birth injury in a further 5 patients. One patient with achondroplasia was found to have a benign tumour, the nature of which was not established, and two patients developed

TABLE 3:1 CHARACTERISTICS AND FOLLOW-UP INTERVALS IN 106 PATIENTS WITH NEWLY DIAGNOSED PREVIOUSLY UNTREATED EPILEPSY

	No (%)
Sex	
Male	51(48)
Female	55(52)
Median Age At Diagnosis(years)	23(Range 6-77)
Seizure Type	
Tonic Clonic Alone	59(55)
Partial Seizures Alone	22(21)
Mixed Seizure Types	25(24)
Pretreatment Tonic Clonic Seizure Frequency	
High	45(57)
Low	34(43)
Aetiology of Epilepsy	
Symptomatic	35(33)
Idiopathic	71(67)
Associated Handicaps	
Neurological	11(10)
Psychiatric	31(29)
Social	27(25)
Family History	
Present	22(21)
Absent	84(79)
EEG Features	
Epileptiform Changes	43(41)
Non-specific Changes	82(77)
Normal	14(13)
Months of Follow-up	
<24	5 (5)
25-48	14(13)
49-72	48(45)
73-96	39(37)
Median Follow-up, months	66 (range, 6-96)
Total	106(100)

gliomas during the course of treatment. One patient had tuberous sclerosis and another had an undiagnosed syndrome with mental retardation associated with a familial neuropathy. Abnormalities were found on CT brain scan in 8 patients which consisted of generalised cortical atrophy in in 3 patients, focal atrophy in 2 patients and enlargement of one temporal horn in a further three patients.

An associated neurological handicap was present in 11 patients. Amongst these patientsp 8 were mentally retarded, 3 had acquired cognitive deficits and 3 patients had a hemiplegia. Thirty one patients developed psychological disorders of sufficient severity to warrant referral to a pyychiatrist. The commonest diagnosis was an affective disorder, usually depressive illness (19 patients), or a pesonality disorder (7 patients). One patient developed anorexia nervosa and two developed psychotic illnesses.

Routine 16 channel pre-treatment EEGs were undertaken prior to treatment in all patients. In 14 patients the resting record and the response to overbreathing and photic stimulation was normal. Forty one patients had epileptic abnormalities which were generalised spike and wave in 8 patients and focal abnormalities, mostly in the temporal region, in the remaining records. Eighty two of the EEGs had

abnormalities of the background rhythms which were classified as minor in 38 instances and moderate or severe in the remaining 44. On completion of the study, eight patients had been lost to follow up after a median of 1.9 years. Five patients were followed for less than two years, 14 patients between two and four years, 48 patients between four and six years and the remaining 39 between six and eight years. The median follow up was six and a half years.

2. Treament Outcome

Sixty one patients were treated with phenytoin and 45 with carbamazepine. Anticonvulsant levels were monitored and the dosage only increased if further seizures occurred with anticonvulsant levels below the optimum range. Patients who experienced two or more seizures despite an optimum anticonvulsant level were considered to have failed on monotherapy and the addition of a second drug was considered. Nine patients continued to have seizures and never achieved an optimum anticonvulsant level despite progressive increases in dosage, presumably because of poor compliance. Twenty one patients failed on treatment, by one year in 13, by two years in 19 and by six years in further two. At the end of the study, after a median follow up of five and one half years, 78 patients were still on monotherapy of whom 70 were taking the original prescribed

drug. Ten patients were taking two drugs and treatment had been discontinued in eighteen. Six patients underwent successful planned anticonvulsant withdrawal and twelve patients stopped treatment of their own accord.

3. First Seizure Recurrence

The majority of patients experienced at least one further seizure after starting treatment. Amongst the 80 patients who had a recurrence 35 did so by two months, 44 by four months, 51 by six months and 62 by one year. One patient was seizure free and lost to follow up at six months.

The actuarial percentage of patients who remained seizure-free by duration of follow-up is shown in Figure 3:1. Fifty per cent remained seizure-free by six months, 40% by one year, 34% by two years, 24% by four years and 21% by eight years.

The pre-treatment tonic clonic seizure frequency had a marked effect on the probability of remaining seizure free after starting treatment. Figure 3:2 shows the actuarial percentage seizure free by duration of follow up for those with a high and low pre-treatment tonic clonic seizure frequency. Not only did those with a high seizure frequency relapse more quickly but 24% remained

FIGURE 3:1 PROGNOSIS IN NEWLY DIAGNOSED EPILEPSY : THE ACTUARIAL PERCENTAGE OF PATIENTS REMAINING SEIZURE-FREE ON TREATMENT

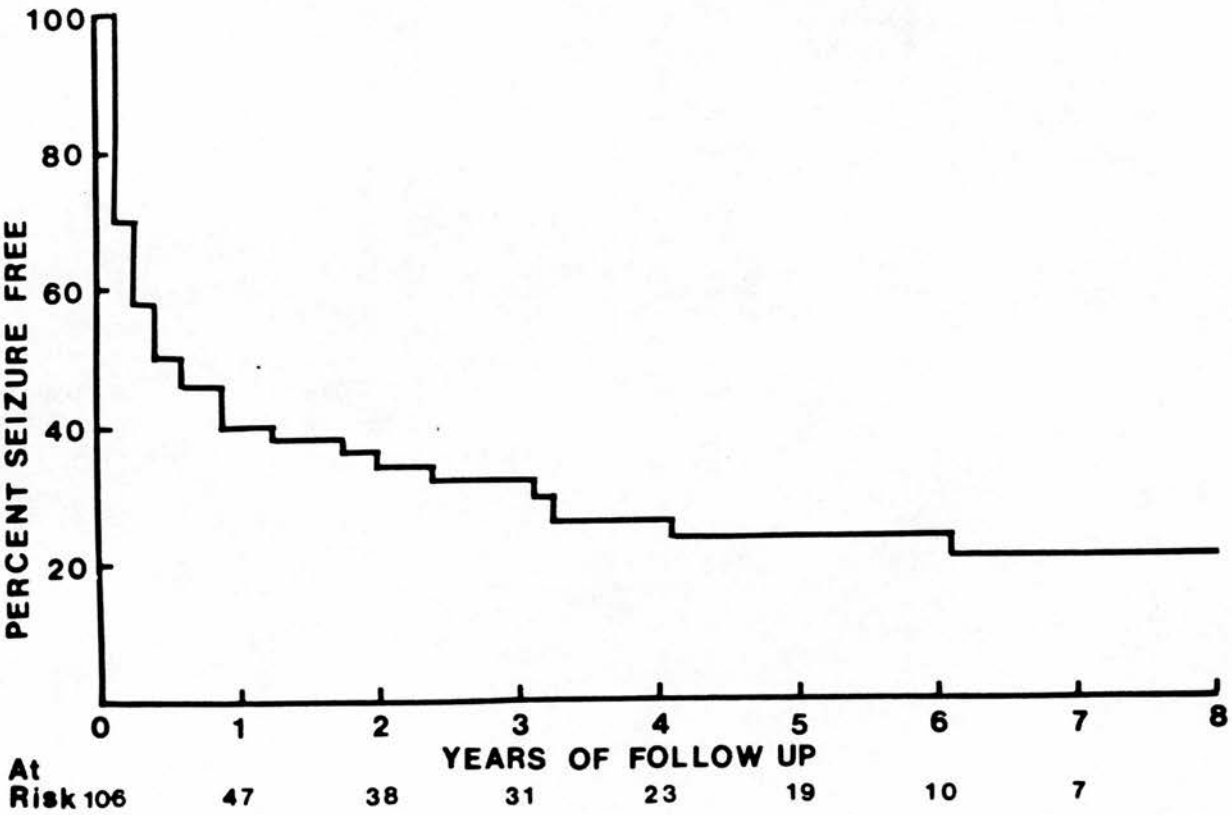
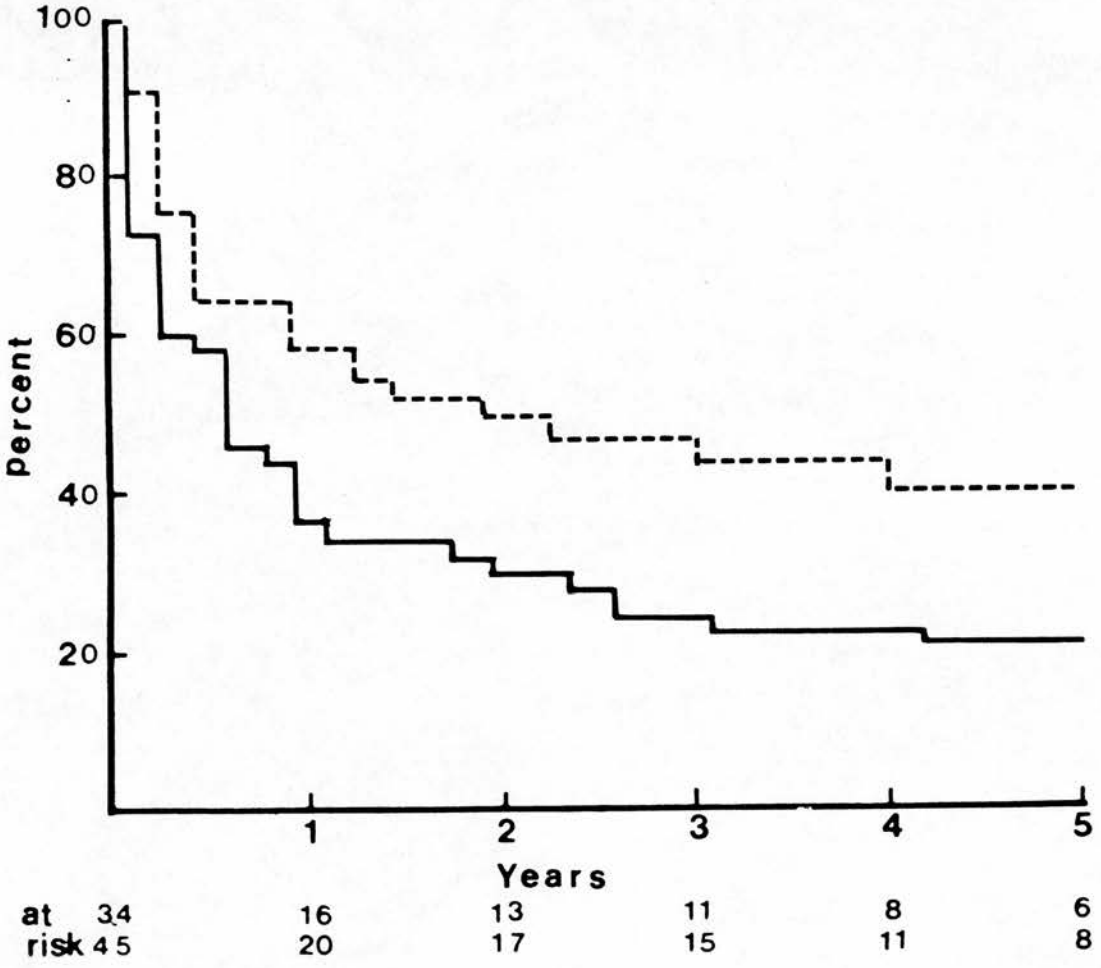


FIGURE 3:2 ACTUARIAL PERCENTAGE OF PATIENTS REMAINING SEIZURE FREE ON TREATMENT: THE INFLUENCE OF PRETREATMENT TONIC CLONIC SEIZURE FREQUENCY



Broken Lines = Patients with a low pretreatment seizure frequency (Less than two seizures per month). N=34

Solid Lines = Patients with a high pretreatment seizure frequency (Two or more seizures per month). N=45

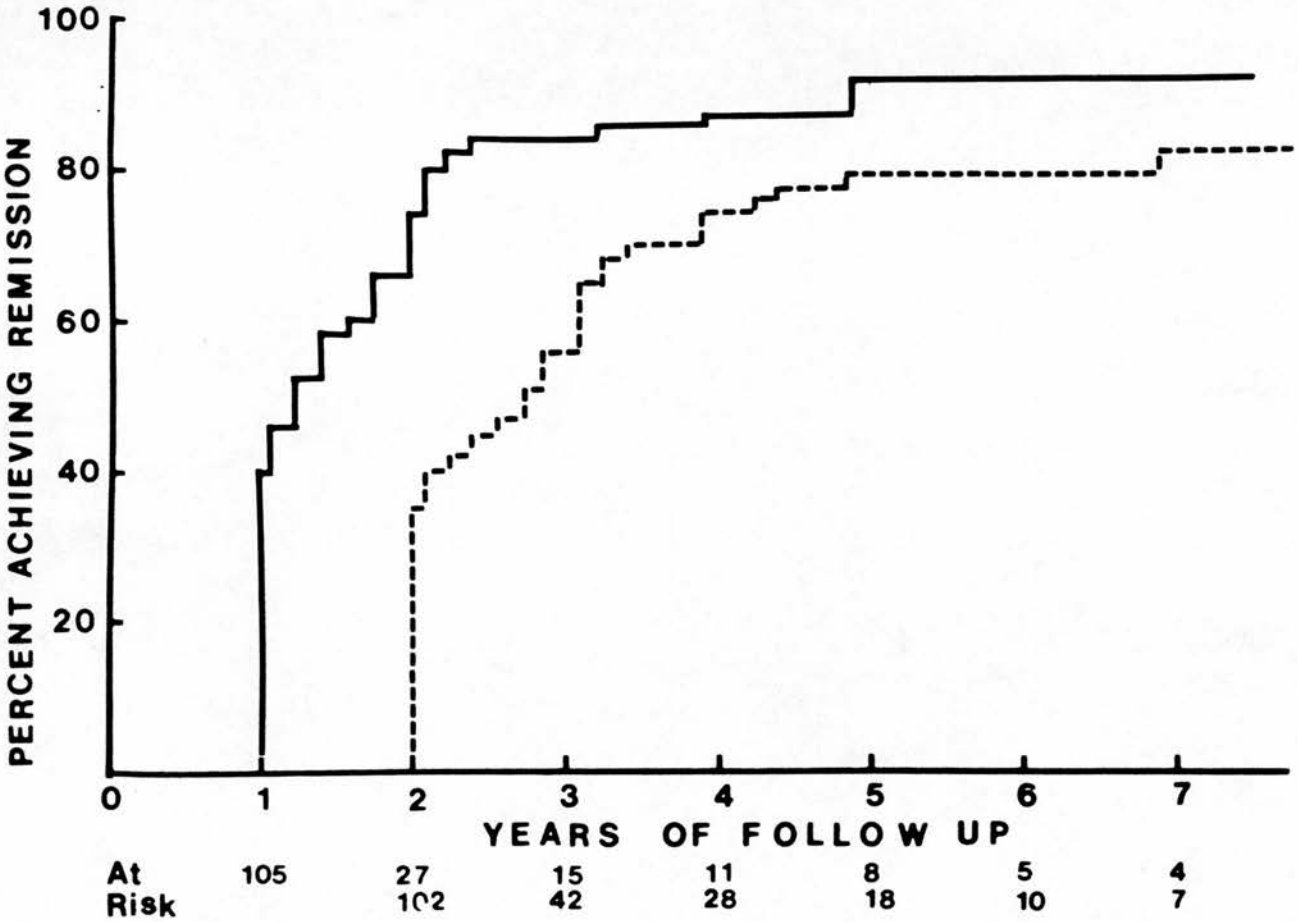
seizure free, compared to 41% amongst patients with a low pre-treatment frequency (χ^2 = 5.44, d.f. = 1, p = 0.02). No other clinical feature was significantly associated with the probability of remaining completely seizure-free from partial seizures, tonic clonic seizures or all seizure types.

4. Seizure Control

The prognosis for seizure control was assessed by analysing the actuarial percentage of patients in whom seizures were suppressed completely for periods of one and two years (Figure 3:3). The figures represent the cumulative probability in actuarial percentages of ever having been seizure free. A one year seizure free period occurred in 40% by one year, in 73% by two years, in 84% by three years, in 88% by four years, and in 89 and 92% by five and eight years respectively. The majority of remissions occurred shortly after starting treatment; at the end of the first year of treatment, 75% of patients who were going to remit were either in or entering a one year remission period.

The results for two year remissions were similar as the majority of patients who were seizure-free for one year subsequently went onto a second year with no seizures. The actuarial percentage of patients achieving two year remission was 35% by two years, 57% by three years, 73% by

FIGURE 3:3 THE ACTUARIAL PERCENTAGE OF PATIENTS SEIZURE FREE FOR ONE AND TWO YEARS



Solid lines = One year seizure-free

Broken lines = Two years seizure-free

four years, 79% by five years and 82% by eight years.

5. Relapse Rates following First Remission

In the previous section the prognosis was determined by analysing the actuarial percentage of patients in whom all seizures were controlled for periods of one and two years. Using this method of analysis, once a remission had occurred, the data relating to further follow up was censored. It was apparent, however, that following remission a number of patients subsequently experienced a seizure relapse.

The numbers of patients achieving one, two, three and four year remission and the subsequent relapse rates for each group are shown in Table 3:2. In the 89 patients who experienced a one year remission, the relapse rate was not inconsiderable. It occurred in 22% by one year of follow up, 32% by two years, 44% by three years and 48% by 4 years. With increasing periods of remission, however, the relapse rate fell such that in patients who had been seizure free for four or more years only 17% experienced a subsequent seizure recurrence.

The prognosis has been examined in more detail in 76 patients who achieved two year remission and in whom further follow up data were available. Relapses occurred in 25 patients. In 17 cases these were isolated events consisting of one or two

TABLE 3:2 THE PERCENTAGE OF PATIENTS EXPERIENCING A RELAPSE AFTER PERIODS OF ONE, TWO, THREE AND FOUR YEARS SEIZURE-FREE

Remission Period (years)	Number of Patients	Number Relapsing N (%)	Actuarial Recurrence Rates at: 1 yr	2 yr	3 yr	4 yr
1	89	29 (33)	22	32	44	48
2	76	25 (33)	14	27	36	39
3	59	11 (19)	17	26	31	31
4	42	6 (14)	8	17	17	17

seizures and in 16 could be directly related to poor compliance with medication. The combined follow up for all 76 patients following the first two year remission was 253 years. If the total follow up period was divided into 2 month intervals then seizures occurred in 52 of these intervals, that is to say only 3% of the total. It appeared that once a two year remission had occurred the prognosis was extremely good and no patient developed intractable epilepsy.

6. Patients Failing to Achieve Remission

Patients who failed to achieve a period of at least one year completely free of all seizures had a uniformly poor prognosis. They were followed for a total of 63.5 years. In a similar manner to the previous section this was equivalent to a total of 376 two month intervals of follow-up. During each of these intervals no seizures occurred on only 39 occasions, or 10% of the total follow-up.

7. Prognostic Factors

An analysis of the factors that were useful in predicting prognosis were performed by comparing the percentages of patients who achieved one year completely free of all seizures. The results are summarised in table 3:3 and figure 3:4. The presence of partial seizures (Log - Rank Statistic: $\chi^2 = 9.1$, d.f. = 2, p = 0.011); a family history of

TABLE 3:3 PROGNOSTIC FACTORS IN 106 PATIENTS WITH NEWLY DIAGNOSED EPILEPSY

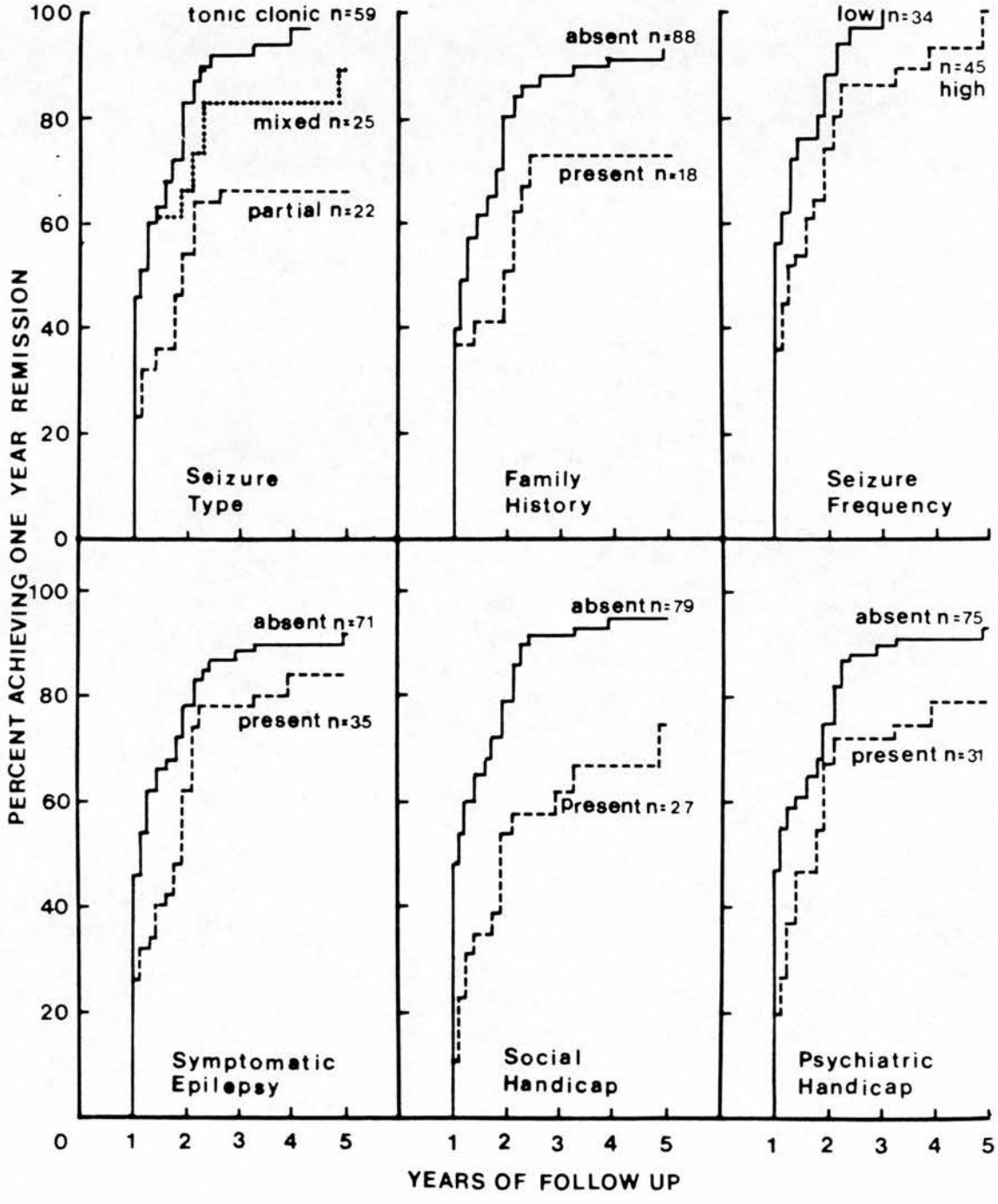
	No(%)	Percentage Seizure-Free at: 1yr	2yr	5yr
Sex				
Male	51(48)	40	77	95
Female	55(52)	48	70	84
Age of Onset (years)				
10-19	33(31)	35	69	83
20-29	28(26)	40	65	81
30+	39(37)	46	71	96
Seizure Type				
Tonic Clonic Alone	59(56)	46	83	97
Partial Seizures Alone	22(21)	23	54	73
Mixed	25(24)	38	66	89
Pretreatment Tonic Clonic Seizure Number				
Two	24(30)	57	65	95
Three	24(30)	54	83	96
Four or More	32(40)	54	83	83
Pretreatment Tonic Clonic Seizure Frequency				
High	45(57)	36	74	93
Low	34(43)	56	88	100
Symptomatic Epilepsy				
Present	35(33)	26	62	84
Absent	71(67)	46	78	92

contd/

TABLE 3:3 Continued.

	No(%)	Percentage Seizure-Free at: 1yr	2yr	5yr
Timing of Seizures				
Nocturnal Only	28(26)	36	88	96
Other	78(74)	40	60	88
Social Handicap				
Present	27(25)	11	54	74
Absent	79(75)	48	79	95
Psychiatric Handicap				
Present	31(29)	20	68	79
Absent	75(71)	47	75	93
Family History of Epilepsy				
Present	22(21)	37	51	73
Absent	84(79)	40	79	93
Pretreatment EEG				
Epileptiform Changes	43(41)	42	69	89
Minor Slow Wave Changes	38(36)	46	87	90
Moderate or Severe Slow Wave Changes	44(42)	27	60	88
All Patients	106(100)	49	73	89

FIGURE 3:4 THE ACTUARIAL PERCENTAGE OF PATIENTS SEIZURE FREE FOR ONE YEAR: PROGNOSTIC FACTORS



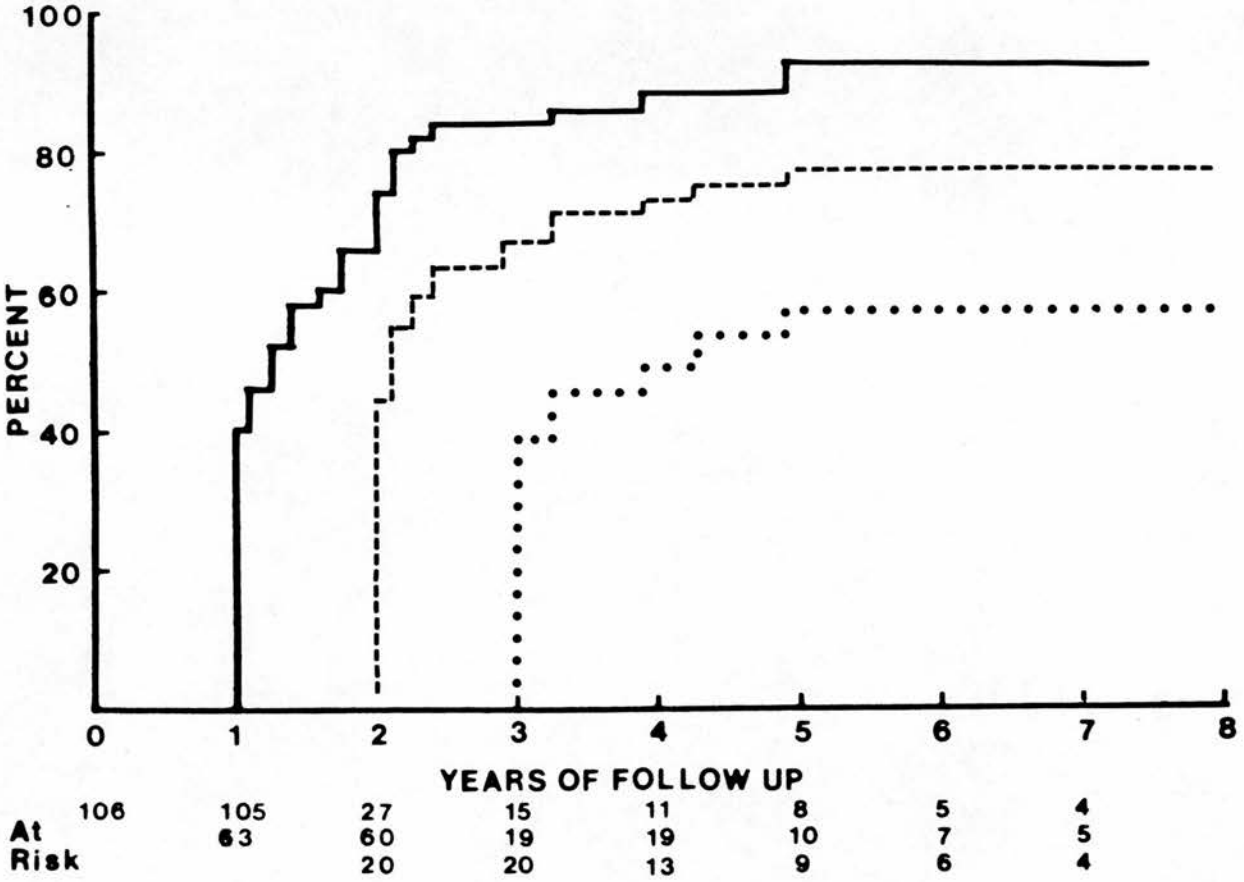
epilepsy (χ^2 = 5.4, d.f. = 1,m p = 0.02); a high frequency of tonic clonic seizures before treatment (χ^2 = 5.3, d.f. = 1, p = 0.02); symptomatic epilepsy (χ^2 = 3.8, d.f. = 1, p = 0..05), or a social (χ^2 = 11.6, d.f. = 1, p < 0.001), or a psychiatric handicap (χ^2 = 4.3, d.f. = 1, p = 0.038) predicted a worse prognosis.

Age at onset of seizures was not of prognostic value. Patient with noctural seizures had a better prognosis and those with a high pretreatment number of tonic clonic seizures tended to do worse but in neither instance did this reach significance. The pretreatment EEG appeared to be of little value in predicting prognosis. The presence or absence of epileptiform features was not associated with outcome. Patients with moderate of severe slow wave abnormalities in the pre treatment EEG tended to respond less well to treatment but this again failed to reach statistical significance.

8. The Early Response to Treatment

The influence of the early response to treatment on subsequent seizure control was also assessed (figure 3:5). Ninety two per cent of all patients achieved a one year period completely seizure free. In 63 patients who had seizures during the first year of treatment, 77% were controlled and in 32 who continued to have seizures during the second year 57% were controlled. If seizures continued

FIGURE 3:5 THE INFLUENENCE OF DURATION OF SEIZURES ON THE ACTUARIAL PERCENTAGE OF PATIENTS SEIZURE-FREE FOR ONE YEAR



Solid lines = All patients from the start of treatment

Broken lines = Patients with seizures in the first year of follow-up

Dotted lines = Patients with seizures in the second year of follow-up

for up to two years after the start of treatment, the probability of a subsequent achieving a remission had fallen by about one half.

9. Poor Compliance with Medication

An assessment of compliance with medication was undertaken in 95 patients in whom adequate data was available. Three criteria were used to identify patients who were thought to comply poorly with medication.

a. Patients who admitted to seizures related to abrupt withdrawal of anticonvulsants on two or more occasions.

b. Patients in whom an optimum anticonvulsant level was never achieved despite progressive increase in dosage.

c. Patients who showed variable anticonvulsant levels whilst taking a constant dose of a drug. Variable drug levels were defined as two or more instances on which the level showed a greater than 50% variation about the mean whilst on any given dosage.

Complete data was available in 95 patients. Using these definitions 15 patients experienced two or more withdrawal seizures, 9 patients failed to achieve an optimum anticonvulsant levels and 29 had varying drug levels whilst on any given dosage. Forty two patients (44%) had evidence of one or more of these factors.

An analysis was undertaken to identify groups of patitnts in whom poor compliance was more prevalent (table 3:4). Sex, age, seizure type, etiology of epilepsy or associated handicaps were not significantly associated with poor compliance. Poor compliance however was commoner amongst patients taking phenytoin and also those who gave a history of one or more episodes of acute anticonvulsant toxicity. Amongst 60 patients taking phenytoin, 33 (55%) showed poor compliance and 9 out of 35 (25%) in those taking carbamazapine ($\chi^2 = 8.86$, $p = 0.01$). Acute toxic effects were recorded in 26 patients of whom 17 (65%) showed poor compliance compared with 25 out of 69 (36%) with no such history ($\chi^2 = 7.69$, $p = 0.01$).

The influence of poor compliance on prognosis was assessed by comparing the actuarial percentage of patients achieving one and 2 years completely free of seizures. There was no significant difference in outcome between the two groups. Poor compliance did, however, appear to be important in determining relapses in patients who were in remission. Of

TABLE 3:4 POOR COMPLIANCE WITH MEDICATION; PREVALENCE AND CLINICAL CHARACTERISTICS AMONG 95 PATIENTS WITH NEWLY DIGNOSED EPILEPSY

Clinical Characteristic	Number of Patients	Poor Compliance
	N	N (%)
Sex		
Male	46	18(33)
Female	49	24(48)
Age of Onset of Epilepsy		
16 years or less	19	9(47)
Over 16 years	76	33(43)
Seizure Type		
Tonic clonic	55	23(42)
Partial or mixed seizurs	40	19(48)
Symptomatic Epilepsy		
Present	37	14(37)
Absent	58	28(48)
Psychiatric Handicap		
Present	27	13(48)
Absent	68	29(42)
Social Handicap		
Present	22	8(36)
Absent	73	34(46)
Drug	60	33(55)
Phenytoin	35	9 (29)
Carbamazepine		
Anticonvulsant Toxicity	26	17(65)
Present	69	25(36)
Absent		
All patients	95	42(44)

the 79 patients who achieved two years completely seizure free, follow up was available in 76. Of these 25 experienced a relapse and in 16 cases this was due to an abrupt withdrawal of drugs. In a further 4 evidence of widely varying anticonvulsant levels was found.

10. Prognosis in Patients Treated with Polytherapy.

Eleven patients who failed on monotherapy were treated with polytherapy for a period exceeding 6 months. Nine patients had initially received phenytoin and two were given carbamazepine. The median duration of follow-up on polytherapy was 2.5 years (range, 0.5 to 5.5 years). Six patients continued to have seizures in every two month interval of follow-up. A further 3 had an initial 2 month seizure free period but subsequently relapsed with an intractable seizure disorder. Two patients achieved a period of at least one year seizure free whilst on polytherapy. Both had complex partial seizures of temporal lobe origin, were started on treatment with phenytoin and within one year were given carbamazepine. It is difficult to reach a firm conclusion on the possible benefits of polytherapy on the basis of these data. The numbers of patients requiring polytherapy was small, treatment decisions were not made on a randomised basis and the statistical analysis did not take account of short term changes in seizure frequency. They do suggest, however, that about one fifth of patients who fail on monotherapy subsequently achieve a prolonged remission of seizures following the addition of other drugs.

D. DISCUSSION

1. Remission Rates in Epilepsy

In this study the prognosis for seizure control in newly diagnosed epilepsy was good. Twenty six patients remained completely seizure free for a median period of 64 months. At the end of follow up the cumulative probability of ever having been two years completely free of all seizures was 82%. After a two year remission had been achieved the subsequent prognosis was good and most patients remained seizure free for as long as they were followed. Relapses, when they occurred, were usually isolated events often related to poor compliance.

The most authoritative and widely quoted work on the prognosis of patients with epilepsy is that published by Rodin (1968). In view of its importance, it was discussed in some detail in Chapter 1. Rodin's initial, and possibly most important conclusion, was that only one-third of all epileptic patients are likely to achieve a terminal remission of at least two years. Rodin based this statement on a review of the literature and the results of the most important prognostic studies have been summarised in Table 1:11. However, if the methodology in each of these studies is subjected to more careful analysis, a number of important deficiencies are apparent.

Difficulties have arisen in the interpretation of previous prognostic studies from a number of causes. These have included retrospective analyses, differing methods of classification and definiition of epilepsy and poor documentation of treatment methods. The single most important consideration, however, has been patient selection. All previous prognostic studies have been based on the cross sectional selection of patients attending specialised epilepsy or neurology clinics; that is to say patients who, at a particular point in time, were attending a clinic or institution for treatment were selected for follow up. The major deficiency of this method is that such clinics or institutions will be strongly biased towards following up patients with chronic epilepsy whose seizures have proved difficult to control.

This can be illustrated by examining the mean duration of epilepsy prior to entry into the follow-up period in some of the prognostic studies that have been undertaken (Table 3:5). In the study by Alstrom (1950) the mean duration of active epilepsy was 13.5 years and only 22% acieved remission. In the others most patients have suffered from epilepsy for periods of at least 2 to 6 years and the outlook is equally poor. Unfortunately a number of authors have not supplied this crucial information and the results are therefore difficult to interpret and have been excluded from the Table. Is is clear from a careful reading of the methodology that

TABLE 3:5 HOSPITAL BASED STUDIES OF THE PROGNOSIS OF EPILEPSY. DURATION OF ILLNESS PRIOR TO INCLUSION OF PATIENTS INTO THE STUDY

Author	Duration of Epilepsy, years	Percentage in Remission
Alstrom, 1950	13.5	22
Strobos, 1959	6	38
Kiorboe, 1960	<5	32
Kuhl et al, 1961	1.25	61
Trolle, 1961	3.2	37
Juul-Jensen, 1963	>2	32
Currie et al, 1971	6	40
Janz, 1972	>2	44
Okuma & Kumashiro, 1981	<5	58

all of them contain a high proportion of cases with chronic intractable epilepsy.

The impact that this form of patient selection may have had is illustrated by the only two studies that have examined prognosis in epilepsy of short duration. Both of these studies showed a considerably better prognosis than that suggested by Rodin(1968). Kiorboe (1960) studied 156 patients with onset of seizures after the age of seventeen. The author stated that, unlike other prognostic studies, patients with epilepsy of short duration (less than five years) were selected. After a follow up of four to seven years 14 had died and 12 were lost to follow up. Of the remaining 130 patients, 41(31%) had been completely seizure free. However, a further 27 patients, after an initial relapse, subsequently became seizure free, giving a final remission rate of 68 out of 130 or 52%. In a further publication Kuhl et al, (1967) added another 60 patients to the original series using a similar method of selection. The mean duration of epilepsy before entering into the study was 1.25 years. One hundred and five patients (61%) had a period of at least one year completely seizure free. The Japanese Multi Institutional Study (Okuma & Kumashiro, 1981) used a similar method of selection to the previous authors, namely a duration of epilepsy less than five years in all patients entered. The authors note that their remission rate of 58% cent was considerably higher than that quoted by Rodin (1968). They

attributed this to advances made in treatment, although no details concerning which methods were actually used were given anywhere in the paper. It is more likely that the favourable outcome was the result of patient selection.

2. Relapse Rates Following Remission of Seizures

In his text Rodin (1968) emphasised the tendency of epilepsy to relapse. Although a period of satisfactory seizure control may occur, the usual course is that after a period of time seizures will recur. Because of the tendency of epilepsy to relapse Rodin thought that the disease was likely to be chronic in as many as 80% of cases.

In contrast to Rodin's conclusion, in the present study all the determinants of outcome showed improving prognosis with increasing duration of follow up. Remission rates, although highest in the first one to two years of treatment, continued to increase on further follow up (see Figure 3:3). It was a striking observation that once a remission had occurred within the first few years the subsequent development of an intractable seizure disorder was most exceptional. Although a third of patients experienced at least one more seizure after achieving two year remission these were almost always isolated events. On prolonged observation these patients only experienced seizures in 3% of the subsequent follow up intervals. Furthermore, in a high proportion of these cases

seizures would be directly related to poor compliance with medication and with increasing duration of remission the probability of experiencing a relapse fell progressively (see Table 3:2).

The present study was based on follow up of patients for periods of up to eight years from the time of initial diagnosis. It is possible that over time a number of cases would have experienced a recurrence of active epilepsy. There are few studies in the published literature that have provided both prolonged follow up and have attempted to carefully document relapse rates. In the retrospective community based survey by Annegers et al. (1979) patients were followed for periods of up to 20 years. Relapse rates were measured by comparing the percentage of patients who had ever been in remission with those whose seizures were controlled at the end of follow up. At no time was the difference between these two figures greater than 10%. Goodridge & Shorvon (1983) in a similar study found that once a remission had occurred it was usually permanent.

If after an initial good response to treatment seizures recur, the possibility of brain tumour must always be considered, particularly if a new seizure type develops. In assessing patients with chronic long standing epilepsy a history of a previous remission of seizures is occasionally obtained. Some patients claim that sometime in the past they

have been seizure free for periods of two, three or more years. In the author's experience this course of events is usually shown to be incorrect following careful scrutiny of the individual case history. Sometimes the initial seizures occurred early in childhood and subsequently prove to have been febrile convulsions. The period of remission may have been in fact a change in seizure type which can occur during the course of chronic epilepsy. A witnessed history subsequently shows that during this supposed period of remission the patient continued to have short lived attacks that were often unnoticed. Prolonged remission of seizures followed by the development of an apparantly intractable seizure disorder may be particularly common amongst patients who are subsequently discovered to have pseudo seizures or in whom poor compliance or alcohol abuse is a cause of the recurrence.

3. Treatment

Treatment has, in general, received only scant attention in prognostic studies. It is apparent that in the retrospective surveys reviewed in Chapter 1 treatment was often undertaken by a number of doctors with no consistent management policy. Many authors (Kirstein, 1942; Kiorboe, 1960; Probst, 1960; Janz, 1972; Ohtahara et al, 1977; Okuma & Kumashiro, 1981; Sofijanov, 1982) made no mention at all of treatment whilst others only give a list of drugs used (Strobos, 1959;

Currie et al, 1971). Serum anticonvulsant level monitoring is only mentioned by Schmidt et al. (1983) yet even here it was apparent that this was undertaken in only a small proportion of patients. This deficiency was even greater in the retrospective community based surveys. Annegers et al. (1979), Sillanpaa (1983) and Brorson & Wranne (1987) make no mention of treatment methods whilst Goodrigde & Shorvon (1983) found that surveillance and audit of treatment was generally poor, drug concentrations rarely measured and that there was, in general, "an insoucient attitude to many aspects of treatment."

Rodin (1968) identified two aspects of treatment which were of crucial importance in determining the prognosis of epilepsy. Firstly the need to monitor anticonvulsant levels such that drugs were used to optimum effect and secondly the impact of poor compliance with medication on seizure control.

a. Anticonvulsant Level Monitoring

In the present study all patients were initiated on treatment with monotherapy with a low starting dosage. Anticonvulsant levels were checked and if seizures continued the dosage was increased until the level was in the optimum range. A second drug was added only if two or more attacks had occurred despite an optimum anticonvulsant level. In those patients

who took their prescribed medication on a regular basis, treatment was, therefore, optimised.

Therapeutic serum levels have now been established for the major anticonvulsant drugs and are in wide clinical usage. In describing the response to treatment in this thesis the term "optimum" rather than "therapeutic" anticonvulsant level has been used. The reason for this is that the optimum treatment for any given patient is not necessarily the establishment of a therapeutic anticonvulsant level. As many as one quarter of patients with newly diagnosed epilepsy achieve complete control of seizures with anticonvulsant levels below the the therapuetic range (Shorvon et al, 1978). Anticonvulsant level monitoring is most firmly established for phenytoin (Chadwick, 1987). This drug displays non linear kinetics (Richens & Dunlop, 1975) and small increments in dosagage can precipitate acute toxic reactions, which on occasion are irreversible (Reynolds, 1975; Dam 1982). In the case of carbamazepine seizure control does not appear to be so closely related to serum concentrations, possibly due to the presence of active metabolites (Troupin, 1983). Serum levels of sodium valproate tend to fluctuate because of the short half life of the drug and there appears to be a delayed onset in effect, that is independant of anticonvulsant levels (Dreifuss, 1983). With both these drugs useful improvements in seizure control without side effects can sometimes be

achieved with anticonvulsant levels above the therapeutic range. Conversly other patients may experience unacceptable toxicity even with levels within the quoted therapeutic range.

Reynolds & Shorvon (1981) have emphasised that anticonvulant level is an important help in avoiding and reducing polytherapy. In patients whose seizures are not controlled on a single drug, blood concentrations will help identify poor compliers and those who are being suboptimally treated allowing the clinician to use the initial drug to maximum effect before attempting to add another. Similarly, in patients already on polytherapy, it is not an uncommon experience that all the anticonvulsant levels are in the suboptimum range. In these patients useful improvements in seizure control occur when one drug is given in the correct dosage and the others are withdrawn.

b. Poor Compliance with Medication

Poor compliance has been identified as a major cause of poor seizure control by a number of authors and the prevalence of this problem is said to be as high as 50% of patients (Kutt et al, 1966, Shope, 1981; Liske & Greene, 1985). These findings were confirmed in the present study. Twenty-nine patients showed 50% variations in anticonvulsant levels on two or more occasions whilst taking the same dosage; 8 patients failed to achieve optimum anticonvulsant levels despite progressive increases in dosage and 15 patients

experienced 2 or more withdrawal seizures. Forty-two patients (42%) had evidence of one or more of the above criteria. Similar evidence of the extensive degree of this problem has been reported in other prognostic studies. Kuhl et al,(1967) found that 75 patients who had poor control of seizures, 40 (43%) either did not take any medication or were inadequately treated. Currie et al, (1971) reported that among 666 patients with temporal lobe epilepsy 75 (12%) took drugs irregularly whilst in the community survey by Sillanpaa (1983) poor compliance was said to have occurred in 27% of patients.

In the present study poor compliance was more common in those patients with a history of anticonvulsant toxicity and also in those taking phenytoin rather than carbamazepine. These results however do not necessarily imply a causal relationship. Because the relationship of dosage to anticonvulsant level appears to be closer for phenytoin than for carbamazepine, variability in drug concentrations may be a more sensitve indicator of poor compliance in patients taking the former drug. Furthermore, in the same way that withdrawal seizures may follow poor compliance, if the dosage is subsequently increased acute toxicity may be precipitated.

The impact of poor compliance with medication on the long term prognosis for the group as a whole proved hard to assess. There was a strong clinical impression that it was

particularly widespread in the early years of treatment in those who failed to respond to monotherapy (Chesterman et al, 1987). In patients whose seizures were poorly controlled there was often a history of missed follow up appointments or that the patient had run out of drugs and failed to obtain a repeat prescription. These patients were often unsure as to the dose of drugs they should be taking or had failed to carry out previous instructions about changes in therapy. Others who claimed to be taking a drug on a regular basis were found to have undetectable serum anticonvulsant levels.

In the present study an attempt was made to use more objective criteria based on anticonvulsant level monitoring. Using the methods described above 42 patients were thought to show significant evidence of poor compliance with medication. It was an unexpected observation that the long term prognosis for seizure control did not differ amongst these patients compared to those who appeared to be taking their medication on a regular basis.

There are two possible reasons for this. Firstly, it is notoriously difficult to identify and quantify the degree of poor compliance in individual patients. It is likely to occur to some extent in all patients and any attempt to divide them into "good" and "poor" compliers is to a certain extent arbitrary. Varying anticonvulsant levels is often a useful clinical measure and has been reported to correlate

well with data obtained from questionaires about poor compliance (Leppik et al. 1980). However this method was not validated by such measures in the present study. Secondly, and of particular interest, it is possible that poor compliance was indeed equally prevalent amongst those whose seizures were satisfactorily controlled. There is evidence to support this as the majority of relapses that occurred after a two year remission had been achieved could be directly related to patients stopping anticonvulsants abruptly against medical advice.

4. Prognostic Factors

There has been little previous analysis in the literature of the factors that are of significance in predicting outcome in newly diagnosed epilepsy. In the present study these were analysed by comparing the actuarial percentage of patients achieving one year completely seizure free. The results have been summarised in Table 3:3. Before considering some of these in greater detail, a number of general observations should be made.

The analysis was based on a relatively small number of patients. It is likely, therefore, that only those factors which were of the greatest importance would reach statistical significance. Some authors (Okuma & Kumashiro, 1981; Shorvon & Reynolds, 1982) have reported that patients who experience

only nocturnal seizures tend to have a better prognosis. In the present study 28 patients experienced attacks only at night. In this group the one year remission rates were 36% by one year, 80% by three years and 96% by five years. In the remaining 78 patients who experienced seizures during waking hours the corresponding remission rates were 40%, 60% and 80%. This difference just failed to reach significance with a p value of 0.09. It would be incorrect, however, to conclude that the timing of seizures has no impact on the prognosis in newly diagnosed epilepsy as this difference might have reached statistical significance with a greater number of patients. Similarly patients with a large number of pretreatment seizures and those with diffuse slowing of background rhythms on the initial EEG tended to do less well on treatment but this again just failed to reach signif-icance.

Although a number of adverse prognostic factors were identified the observed differences in outcome between the groups was relatively small. For example seizure type was found to be one of the most important factors in determining the response to treatment. In patients with tonic clonic seizures the remission rates were high, with 96% achieving remission by 5 years of follow up; in those with a low pretreatment seizure frequency remission rates were 100%. Patients with partial seizures had a significantly poorer outcome yet even here the response was by no means

unsatisfactory with 73% achieving remission (compare with the results of Schmidt et al, (1983) shown in Table 1:12).

Despite these difficulties the analysis gave a clear picture of the type of patient who tended to respond poorly to treatment at the onset of epilepsy. Patients with partial or mixed seizure types and those with symptomatic epilepsy and associated neurological, social and psychiatric handicaps tended to do less well. It should be noted that these adverse prognostic factors often occurred together in the same patient. In patients with partial and mixed seizure types there was a high incidence of symptomatic epilepsy. These patients were more likely to have associated neurological deficits. In addition to seizures these patients could be handicapped by cognitive impairment and were prone to develop psycological disorders and social dificulties. Although the overall prognosis in epilepsy is good because of the high prevalence of the disorder these patients accumulate in considerable numbers in specialised epilepsy clinics. In contrast to the controversy surrounding the prognosis for seizure control, there has been a reasonable degree of agreement in the literature on the nature of these adverse prognostic factors. Shortly after the introduction of bromides it became apparent that the response to treatment was not uniform. Gowers (1881) noted that patients with minor seizures and those with symptomatic epilepsy and associated neurological deficits tended to do less well. The adverse

factors described above are in good agreement with those identified by Rodin (1968) to be important in predicting prognosis in chronic epilepsy (see page 87). Similarly in newly diagnosed epilepsy the sex of the patient is of little use in predicting prognosis. Although the initial EEG may be of considerable help in diagnosing specific epileptic syndromes such as the benign partial epilepsies the overall prognostic use of the first record is limited.

The posibility that prognosis may be better in children has been commented upon since antiquity and continues to be a source of controversy in the modern literature. A particular problem has been the heterogenicity of childhood epilepsy where a number of syndromes have been identified which collectively are not uncommon and where the prognosis is known to differ widely (see page 94). The prognostic study described in this Chapter was based upon patients attending an adult neurology clinic. As might be expected the great majority of cases develped eilepsy either in adolescence or adulthood. Only limited conclusions relating directly to the impact of age of onset on prognosis can be drawn from these results. Amongst the 61 patients in whom epilepsy developed during the second and third decades of life a little over 80% achieved remission by eight years of follow-up. The corresponding figure for those patients who were aged 30 or over at the time of the first seizure was 96% but this difference did not reach statistical significance.

Rodin (1968) found that many authors reported that prognosis tended to be worse in epilepsy arising in childhood. This conclusion, however, is open to criticism due to the selected nature of the material studied. Patients with chronic intractable seizures accumulate in epilepsy clinics and the longer the disease has continued the less likely it is to remit. As the majority of prognostic studies have been based on patients attending adult clinics those with childhood onset will have tended to have had the longest history of active epilepsy and subsequently a worse prognosis. Because of this form of patient selection cross sectional studies based on adult populations are unlikely to give reliable results on the influence of age of onset on prognosis. Nowhere has this been more apparent than in prognostic studies of petit mal, the most widely studied childhood epileptic syndrome. As was shown in Chapter one (see page 99) many of these studies included a high proportion of cases who were over the age of 15 at time of entry leading to a strong bias in favour of those patients in whom the disease remained active into adulthood.

There appear to be only two prognostic studies available in the literature which have included both adults and children, and which have avoided the selection bias of including a high proportion of chronic cases. In the Japanese Multi Institutional Study (Okuma & Kumashiro, 1981) patients aged betwen 1 and 4, and those between 5 and 9 years of age had

remission rates of 73 and 69% respectively. In the second and subsequent decades, the percentages were in the order of 50%. The difference in outcome was highly significant. Annegers et al. (1979) found that in those with idiopathic tonic clonic seizures the remission rates were those under the age of 10 was 75%, 68% for those betwen 10 and 19 and 63% for adult onset cases. If those who were in remission and off medication were considered the difference was more striking being 51%, 40% and 28% for the same age groups respectively. It is possible, however, that this may have been a reflection of a greater willingness to withdraw medication in children. Although neither of these studies attempted to take account of the heterogenicity of childhood epilepsy they both suggest that epilepsy arising before the age of ten may indeed have a significantly better prognosis.

5. Statistical Analysis

The analysis of prognosis presented in this Chapter was based on the prolonged prospective follow up of patients for periods of nearly a decade. Such prolonged follow up generates a considerable volume of data on the patterns of seizure occurence. Furthermore the outcome in terms of seizure control was higly variable. Some patients appeared to experience only a few seizures in total. After starting treatment a prolonged and sometimes permanent remission

occurred. In others epilepsy developed into a prolonged intractable illness with seizures occurring in every interval of follow up. In some cases of chronic epilepsy seizures could come in clusters and a short period of satisfactory control was followed by a relapse. It is a formidable problem to develop appropriate statistical methods to analyse these data.

In the present study the total follow up period was divided into two month intervals and patients were designated as being with or without seizures for each interval of follow up. This was done for partial seizures, tonic clonic seizures and all seizures combined (see Appendix 4). Patients who had active epilepsy were usually seen in the outpatients department every two to three months. In addition the data was gathered prospectively and at each visit a careful note of the total numbers of each seizure type were recorded.

In the analysis of outcome widespread use was made of actuarial statistics. The method of derivation of the survival curve has been described in detail in Chapter 2. The application of actuarial statistics to these data has a number of advantages. Firstly different end points or "events of interest" can be measured. In assessing prognosis in newly diagnosed epilepsy the most useful were thought to be first seizure recurrence on treatment and remission rates of one and two years. As the median follow up was five and a half years and most patients were entering remission during

the first two years of treatment it was not possible to examine longer periods of remission with any accuracy. Another advantage of actuarial statistics is that it measures the time taken for the first ever event of interest to occur. The survival curve therefore shows the temporal relationship of remission to follow up. This is a considerable advantage over measuring terminal remission rates, the most widely used determinant of outcome in previous prognostic studies (Rodin, 1968). The analysis also takes account of variable follow up as the percentage of patients achieving the event of interest is derived from the total number who are at risk. Allthough the application of actuarial statistics to the data presented in this Chapter was in general satisfactory, during the analysis a number of deficiencies became apparent.

Survival curves, as their names suggests, were developed to analyse death rates. Once the event of interest, that is to say death, had occurred the further outcome is not of course considered. This is not the case, however, when measuring remission rates in epilepsy. Following one year remission as many as 48% of patients experienced a relapse. This figure decreased progressively with increasing periods of remission (See Table 3:2). Although relapses were usually isolated events they are an important element in the prognosis of epilepsy. The use of actuarial statistics also failed to give any information on the outcome of patients who never achieved remission. These are an important group of patients

as many are likely to develop intractable epilepsy.

On the basis of the data presented in this chapter a novel statistical model was developed in an attempt to overcome some of the difficiencies inherent in actuarial analysis (Johnson et al, 1987). The model involves defining three clinically relevant "states" or outcomes. Firstly remission of seizures were defined as one or more years completely seizure free; patients in this group are likely to have a very good outcome and in a significant proportion treatment may be curative. Secondly, continuous seizures where attacks occur in every interval of follow up; in this group a high proportion may develop intractable epilepsy. The final group, defined by exclusion, are those with intermittent seizures and probably contains a high proportion of cases who comply poorly with medication. The mathematical details of the model have been described elsewhere (Johnson et al, 1987; Johnson et al, in preperation) but in essence the probability of transfer between each of the states is measured and then applied to the initial distribution of patients for each interval of follow up using a Markov chain (see also Loiseau et al 1983). The model predicted that at the end of follow up 70% of patients remitted, 10% had continuous seizures and the remaining patients had intermittent seizures. The chief advantage of this model is that it takes account of variable follow up and also allows patients to transfer between states thus taking account of

the highly variable outcome in epilepsy. The model could be extended to include different seizure types and take account of variable prognostic factors or treatment regimens.

The development of appropriate statistical methods for analysing seizure control in newly diagnosed epilepsy is of considerable importance. In recent years anticonvulsant trials are, for the first time, being undertaken in this group of patients. There are a number of theoretical and practical advantages of such a study design (see page 45 et seq.) and it is likely that an increasing number will be under- taken. It has been traditional in anticonvulsant trials to measure changes in seizure frequency usually on the basis of short periods of follow up. The results are often given as the proportion of patients who experience a 50% or greater reduction in seizure frequency (see for example Callaghan et al. 1985). In newly diagnosed epilepsy such a measure is not only inadequate but fails to give a sensible summary of the data or differentiate between long and short term control of seizures. The recruitment and follow up of into patients entered into these trials is a major undertaking and it is of crucial importance that appropriate statistical methods are developed for analysing the results. A similar consideration applies to recent proposals in which the effects of early and delayed treatment on the long term prognosis of epilepsy would be studied (see chapter 6). The hypothesis under consideration

is whether early treatment in any way improves the subsequent prognosis and reduces the number of patients developing chronic epilepsy. The analysis of such a trial and in particular the methods used to take account of the highly variable outcome in epilepsy would need carefull consideration.

6. The Early Response to Treatment

Perhaps the most striking observation to arise from the present study has been the importance of the early response to treatment in determining the long term prognosis in epilepsy. This is shown by examining remission rates for all the patients in Figure 3:3. The curves relate to the percentage of patients achieving a period of one or two years completely seizure free. It is apparent that the great majority of patients who were going to remit did so early in the course of the disorder. Seventy-five per cent of all patients who were going to remit were entering or in remission during the first year of follow up. As a consequence the longer the seizures continued the less likely was it that a remission would occur (Figure 3:5). If a patient was still having seizures up to two years after the start of treatment the chances of achieving a subsequent remission had fallen by about one half. This observation raises the question as to whether more effective treatment

at the onset of the disorder might improve the subsequent long term prognosis.

All prognostic studies in epilepsy have shown that the longer seizures continue the harder they are to control. This was commented upon even in the Hippocratic writings (see page 78). Gowers (1881) found that the prognosis of epilepsy was in inverse proportion to the duration of the disease, a conclusion that was in agreement with all writers on the subject. He went on to examine this aspect of the natural history of epilepsy in some detail (see Table 3:6). In patients with a duration of illness lasting less than a year 83% had their seizures arrested, results remarkably similar to those given in this Chapter. When untreated seizures had occurred for between 1 to 5, 5 to 9, and over 10 years the proportion of patients who responded to treatment fell progressively to 73%, 69% and 60% respectively. Rodin(1968) made a similar observation in his review of the modern prognostic literature. All authors were in agreement that the longer the illness had lasted the less likely was it that remission would occur. Furthermore the greater the number of seizures prior to the first visit to the physician the less likely was it that complete control would subsequently be obtained (see Table 3:6).

Since all the patients studied here were treated it is impossibe to tell whether this represents the natural

TABLE 3:6 THE INFLUENCE OF DURATION OF ILLNESS ON THE PROGNOSIS FOR SEIZURE CONTROL IN EPILEPSY

(a). Adapted from Gowers, 1881.

Duration of illness	Percentage	
	Unimproved	Arrested
Less than 1 year	17	83
1 to 4 years	27	73
5 to 9 years	31	69
10 years or over	40	60

(b). Adapted from Rodin, 1968.

Initial evaluation after onset of illness	Percentage in two year remission
Within first year	85
Within second year	50
Within third year	33
Within fourth year	28
From 5 to 10 years	36
More than 10 years	13

history of the disorder or whether early control may indeed affect the long term prognosis. Evidence for this possibility could only be obtained from a randomised study involving an untreated control group. Little is known about the natural history of untreated epilepsy. Gowers stated over a century ago that "spontaneous cessation of the disease is an event too rare to be reasonably anticipated in any given case." There is no further information in the literature on this aspect of prognosis which will be considered in greater detail in the next chapters.

E. SUMMARY

1. The prognosis for seizure control has been assessed in a group of 106 patients who were referred to an adult neurology clinic with previously untreated tonic clonic, partial and mixed seizure types who were followed prospectively for a median of 66 months (range 6 - 96).

2. Patients were treated with phenytoin or carbamazepine monotherapy on a nonrandomised basis. Anticonvulsant levels were monitored and the dosage increased if further seizures occurred with anticonvulsant levels below the optimum range.

3. At the end of follow up 78 patients were still on monotherapy of whom 70 were taking the originally prescribed drug. Ten patients were taking two drugs and 18 patients discontinued treatment, 12 of them against medical advice.

4. Twenty-one patients experienced 2 or more seizures despite an optimum anticonvulsant level and were considered to have failed on monotherapy. Thirteen patients failed by 1 year of follow up, 19 by 2 years and all of them by 6 years. Nine patients continued to have seizures with suboptimal levels despite progressive increases in dosage presumably because of poor compliance.

5. The total follow up period was divided into two-month intervals and patients were designated as being with or without partial seizures or tonic clonic seizures or any seizure type for each interval of follow up. The percentage of patients experiencing at least one seizure on treatment and the percentage achieving one and two year remissions were analysed using actuarial statistics.

6. The majority of patients experienced at least one further seizure after starting treatment most within a period of 1 year. Fifty per cent occurred by 6 months of follow up, 60% by 1 year, 66% by 2 years, 76% by 4 years and 79% by 8 years.

7. Patients with a high pretreatment tonic clonic seizure frequency were more likely to experience a further seizure on treatment. No other clinical or investigative feature was significantly associated with the probability of remaining seizure free on treatment.

8. The prognosis for seizure control was assessed by measuring the actuarial percentage of patients achieving a period of 1 or 2 years completely seizure free. A 1 year seizure free period occurred in 40% by 1 year, in 73% by 2 years, in 84% by 3 years, 88% by 4 years and 89% and 92 % by 5 and 8 years respectively. Most patients who achieved a 1 year remission subsequently went on to a second year seizure

free, the remission rates at 8 years of follow up being 82%.

9. Amongst the 89 patients who achieved a 1 year remission the probability of relapse was 48% by 4 years of follow up. In patients who were in 2,3 or 4 remission the relapse rate fell progressively to 39%, 31% or 17% respectively.

10. In three-quarters of cases, relapse were isolated events often related to poor compliance with medication. Once a two year remission had occurred no patient developed an intractable seizure disorder.

11. Twelve patients failed to achieve a one year remission. In this group the outcome was poor, with seizures occurring in 90% of the two month follow up intervals. This group probably corresponds broadly to those with intractable seizure disorders.

12. Prognostic factors were analysed by comparing the actuarial percentage of patients achieving a one year period completely seizure free. Patients with partial or mixed seizure types, a high pretreatment tonic clonic seizure frequency, symptomatic epilepsy, associated psychological or social handicaps and those with positive family history of epilepsy had a significantly poorer outcome. Age of onset of epilepsy, the timing of seizures, pretreatment tonic clonic seizure numbers and the features on the pretreatment

EEG were not significantly associated with prognosis.

13. The early response to treatment was of crucial importance in determining the longer term prognosis. Seventy five per cent of remissions began within the first year of treatment. The longer seizures continued the less likely was remission to occur. In patients who continued to have seizures during the second year of treatment the probability of subsequently ever achieving remission had fallen by about one half.

14. Poor compliance with medication was assessed on the basis of the occurrence of withdrawal seizures, failure to achieve an optimum anticonvulsant level in the face of active epilepsy and increased dosage and variability of anticonvulsant levels whilst on a given dose of a drug. Forty-patients had evidence of one or more of these factors. Patients who were taking phenytoin and those with a history of one or more episodes of acute toxicity showed a higher incidence of poor compliance. It was not possible to document an adverse effect of poor compliance on prognosis, possibly because it was equally prevalent amongst those whose seizures were well controlled.

CONCLUSIONS

1. The prognosis for seizure control in newly diagnosed epilepsy is good. As many as 80% of patients rapidly enter a prolonged period of seizure control most within a year of starting treatment. Relapses are usually isolated events often related to poor compliance and the longer the period of remission the lower the probability of experiencing a further seizure.

2. Previously prognostic studies of epilepsy have all been based on the cross sectional selection of patients attending specialised neurology or epilepsy clinics and have given an unduly gloomy view of prognosis. Patient selection is the single most important reason for the controversy surrounding the prognosis in epilepsy.

3. Patients with partial seizures, a high initial seizure frequency, symptomatic epilepsy and associated psychological and social handicaps have a significantly worse prognosis at the onset of the disorder. This finding is in good agreement with the prognostic factors identified in patients experiencing a recurrence following a first seizure, in determining outcome in chronic epilepsy and in predicting relapse rates following anticonvulsant withdrawal. Although only one quarter of patients with these adverse prognostic

factors failed to respond to treatment because of the high prevalence of epilepsy they accumulate in considerable numbers with chronic intractible seizure disorders.

5. The early response to treatment is of crucial importance in determining the long term prognosis in epilepsy. Seventy five per cent of all remissions occur within the first year of treatment, and the longer seizures continue the harder they are to control. The natural history of untreated epilepsy is largely unknown but these findings raise the possibility that more effective treatment at the onset of the disorder might improve the subsequent long term prognosis of epilepsy.

CHAPTER FOUR

PROGNOSIS FOLLOWING A FIRST TONIC CLONIC SEIZURE

A. INTRODUCTION

Epidemiological surveys have shown that as many as 5% of the population will experience at least one afebrile seizure at some time during their life (Hauser & Kurland, 1975). The patient who presents with a single seizure is a common clinical problem yet the outcome in this group of patient has received only scant attention in the published literature. This has led to continuing uncertainty concerning the subsequent prognosis for seizure recurrence, a lack of clear data on the nature of possible adverse prognostic factors and widely differing treatment policies (Reynolds, 1984).

In this Chapter an analysis of the probaility of seizure recurrence will be presented in a consecutive series of 214 patients who were consecutively referred to a neurology out patients department because of recent onset of tonic clonic seizures. The study was undertaken with the following aims:

i. To analyse the prognosis for seizure recurrence following a first tonic clonic seizure.

ii. To identify factors that are of prognostic importance in predicting a seizure recurrence.

B. PATIENTS AND METHODS

The patients studied were all consecutivly referred to the adult neurology clinic at Kings College Hospital over a five year period between 1978 and 1983. During this period a total of 328 patients were seen who had experienced one or more previously untreated seizures. Cross-sectional selection was avoided in that patients already attending the department for treatment of epilepsy were not considered. Some patients, although presenting with recent onset of seizures, gave a history of one or more attacks, often occuring many years previously. These were considered for inclusion only if they had never previously received anticonvulsant medication.

The following groups of patients were excluded from the study; patients with evidence of a progressive neurological disorder apparent at the time of first diagnosis; those with seizures occurring in the context of acute central nervous system disorder such as meningitis or stroke; patients with significant metabolic disorders such as hypoglycaemia or uraemia; seizures caused by drugs or occurring in the context of alcohol dependence. Patients

who gave a past history of febrile convulsions and subsequently presented with a history of apparently unprovoked seizures were included. Those who had previously experienced attacks relating to any of the factors listed above were, however, excluded.

After exclusion of the above categories a total of 286 patients remained. Seventy two patients had myoclonic, petit mal or partial seizures without secondary generalisation. These patients had almost invariably experienced multiple attacks that could not be accurately dated at the time of first assessment in the outpatients department. The remaining 214 patients with tonic clonic seizures form the basis of this study.

At the time of first assessment in the neurology outpatients department a history and examination were undertaken in the usual manner. A description of the seizure type, the dates of the first and second seizures, the past medical, social and psychiatric history, the results of general and neurological examination and of pretreatment investigations were recorded on a proforma for each patient (see Appendix 1). The clinical details and follow up data for all 214 patients are given in Appendix 5. The number of seizures the patient had experienced at the time of very first presentation was recorded. This information was obtained retrospectively from interviewing

the patient and from the general practitioner's or casualty officer's letter. In a significant proportion of cases the patient presented initially with a single seizure, either to their general practitioner or a casualty department, but had subsequently developed epilepsy when first seen at the neurology outpatients department.

In analysing the prognosis after a first seizure the following definitions were used. A first seizure was defined as the first ever afebrile tonic clonic seizure. Multiple seizures occurring within 24 hours were considered to be a single episode. Patients with a previous history of other seizure types such as partial seizures that had previously gone unrecognised or petit mal attacks in childhood were not included. A second seizure was defined as the next seizure that occurred, whether partial or generalised.

It was the policy of the department, throughout the period of the study, not to treat patients who had experienced only one seizure. A few patients were started on treatment by their general practitioner or by a casualty officer and were still taking medication at the time of first assessment at the hospital. In others, particularly children in whom the initial convulsion was prolonged, treatment was started immediately following the first attack.

Patients who, in December 1983, had been discharged from follow-up and had still experienced only one attack were recalled to the clinic to assess recurrence. If the patient failed to attend, a letter was sent to their general practitioner requesting further information. Thirty seven patients were lost to follow up after a median interval of three and a half months. The follow-up period was divided into one month intervals, starting from the time of the first seizure. The probability of seizure recurrence was assessed using Kaplan Meier survival curves (Kaplan & Meier, 1958). Prognostic factors were assessed by comparing the actuarial percentage of patients experiencing a seizure recurrence. Significance values were based on the log rank test (Peto et al, 1977).

C. RESULTS

1. Patient Characteristics

The characteristics of the 214 patients with tonic clonic seizures are shown in Table 4:1. Just over half the patients were male. Sixty four patients (30%) were aged 16 or less, the median age at first seizure being 22 years. Thirty patients (14%) had symptomatic seizures. The commonest aetiology was cerebrovascular disease. Eight patients had a history of completed stroke which in two cases were due to emboli secondary to congenital heart disease. In a further four patients evidence of focal or generalised atrophy was seen on CT brain scan. One of these gave a history of transient ischaemic attacks, one was diabetic and two were hypertensive. Six patients had a history of birth injury and another six had previously experienced a significant head injury. A tumour was the cause of seizures in four patients. One experienced a seizure twelve months after removal of a convexity menningioma. In two patients mass lesions were found incidentally on CT scan, both of which were thought to be benign. A further patient developed signs of raised intracranial pressure three months after a first tonic clonic seizure and was subsequently found to have a glioma. Two patients gave a past history of menningitis.

TABLE 4:1 CLINICAL FEATURES OF 214 PATIENTS WITH TONIC CLONIC SEIZURES SEEN CONSECUTIVELY AS NEW REFERRALS OVER A FIVE YEAR PERIOD. A COMPARISON OF PATIENTS WITH SINGLE SEIZURES AND THOSE WITH EPILEPSY.

Clinical Charactetistics	All patients	One seizure	Epilepsy
	N (%)	N (%)	N (%)
All Patients	214	64 (30)	150 (70)
Male	112	32 (29)	80 (71)
Female	102	32 (31)	70 (69)
Median Age at First Seizure, Years(range)	22	22 (4-74)	18 (2-78)
Age at First Seizure,			
= or < 16 years	64	10 (16)	54 (84)
> 16 years	150	54 (36)	96 (64)
Symptomatic Seizures	30	5 (17)	25 (83)
Neurological Handicap	22	6 (27)	16 (73)
Family History of Epilepsy	20	5 (25)	15 (75)
Nocturnal Seizures	42	11 (26)	31 (74)
EEG performed	169	49 (29)	120 (71)
Normal Record	63	19 (30)	44 (70)
Epileptiform	47	13 (28)	34 (72)
Non-specific	80	20 (25)	60 (75)
Follow-up (months)			
1 -12	77 (36)*	42 (66)*	35 (23)*
13-24	45 (21)	12 (19)	33 (22)
25-36	31 (15)	6 (9)	25 (17)
37-48	20 (9)	4 (6)	16 (11)
>48	41 (19)	0 (0)	41 (27)
Median Follow-up, Months, (range)	21 (1-228)	8 (1-61)	26.5 (1-228)

* percentages refer to all patients

An associated neurological handicap was present in 22 cases (10%). Seven patients had cognitive deficits of whom three were mentally deficient and four had an acquired dementing illness. Twelve patients had a hemiparesis which had been present since birth in five cases. One patient was deaf and dumb, one had choreoathetosis and one had a right hommonomous hemianopia.

Twenty patients (9%) gave a family history of epilepsy in first degree relatives and 42 (20%) had experienced all their seizures during sleep. An initial EEG was undertaken in 169 patients (79%). In 63 patients (37%) the record was normal, 47 (28%) showed epileptiform abnormalities and in 80 of the records (47%) there were non specific slow wave changes. Seventy-seven patients (36%) were followed for between 1 and 12 months, 45 (21%) for between 13 and 24 months, 20 (9%) for between 37 and 48 months, and 41 patients (19%) for more than 4 years. The median follow up from the time of the first seizure was 21 months.

At the end of the study 64 patients, or 30% of the total had experienced only a single seizure and 150 (70%) had 2 or more attacks. The clinical characteristics of these two groups are shown in Table 4:1. Patients who had experienced a single seizure were followed for a shorter period of time, but otherwise the two groups did not appear to differ in any major respect. Amongst patients who were

aged 16 or under, 16% had a single seizure and 84% developed epilepsy. Similarly amongst patients who experienced symptomatic seizures 17% had a single attack and 83% had recurrent seizures. Both these differences were significant at the level $p < 0.001$ (Pearson χ^2 Test).

2 The Prognosis for Seizure Recurrence in Patients Presenting Following a First ever Seizure

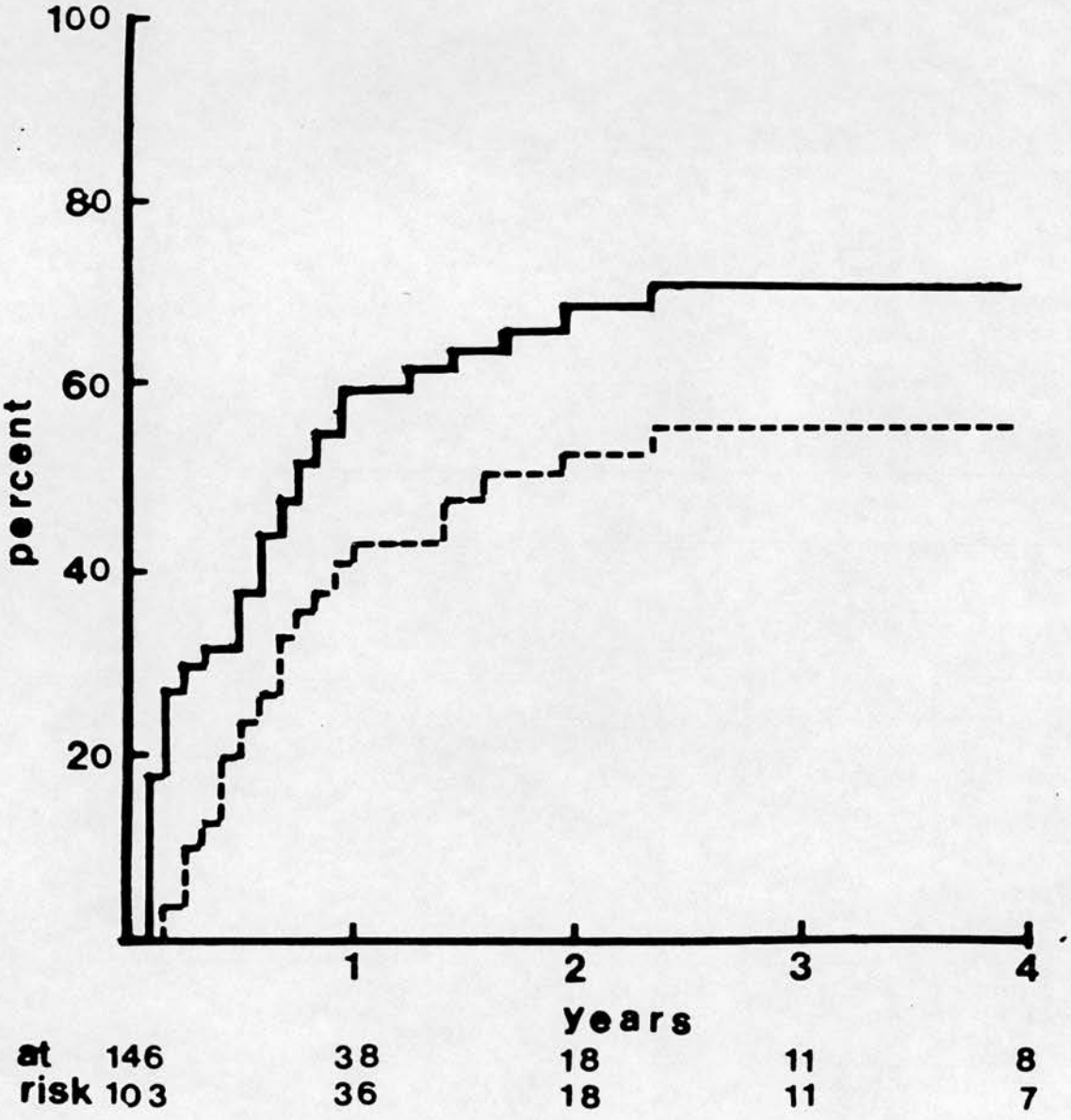
Out of the 214 patients with tonic clonic seizures, 146 presented to medical attention following a first ever seizure. Eighty were seen in the Accident and Emergency Department and 66 by their Family Practioner. The median interval from first seizure to first presentation was one day. The clinical characteristics of the patients are shown in Table 4:2. After a median follow up of 15 months the cumulative probability of seizure recurrence was 19% by one month, 30% per cent by three months, 44% by six months, 60% by one year, 69% by two years and 71% by three and four years (see Figure 4:1).

Patients were seen in the neurology outpatients department at a median interval of one month from the time of the first seizure. During this interval 43 of the original 146 patients had already experienced a seizure recurrence. The clinical characteristics and prognosis in the remaining 103

TABLE 4:2 CLINICAL FEATURES OF PATIENTS WHO PRESENTED FOLLOWING A FIRST EVER TONIC CLONIC SEIZURE; PATIENTS AT INITIAL PRESENTATION (N=146) AND PATIENTS SEEN IN THE NEUROLOGY OUTPATIENTS DEPARTMENT (N=103).

	At Initial Prenentation N (%)	At Neurology Outpatients N (%)
Male	79 (54)	52 (50)
Female	67 (46)	51 (50)
Median Age at First Seizure, Years (range)	21 (2-78)	22 (4-74)
Age at First Seizure,		
= or < 16 years	41 (28)	26 (25)
> 16 years	105 (72)	75 (75)
Symptomatic Seizures	20 (14)	12 (12)
Neurological Handicap	13 (9)	9 (9)
Family History of Epilepsy	12 (8)	7 (7)
Nocturnal Seizures	29 (20)	18 (17)
EEG performed	115 (79)	88 (81)
Normal Record	49 (43)	33 (32)
Epileptiform	27 (23)	20 (19)
Non-specific	50 (43)	38 (37)
Follow-up (months)		
1 -12	65 (45)	45 (44)
13-24	36 (25)	27 (26)
25-36	18 (12)	12 (11)
37-48	13 (9)	9 (9)
>48	14 (10)	10 (10)
Median Follow-up, Months, (Range)	15 (1-69)	15.5 (1-69)
Totals	146 (100)	103 (100)

FIGURE 4:1 CUMMULATIVE PROBABILLITY OF SEIZURE RECURRENCE IN PATIENTS PRESENTING FOLLOWING A FIRST EVER TONIC CLONIC SEIZURE



Solid lines = Patients seen within a median interval of one day following the first seizure

Broken lines = Patients seen within a median interval of one month following a first seizure

patients is shown in Table 4:2 and Figure 4:1 respectively. The cumulative probability of seizure recurrence was 10% by three months, 24% by six months, 44% by one year, 53% by two years and 56% by three years.

3. Treatment

Thirteen patients were treated following the first seizure, of whom five (38%) experienced a recurrence. In the remaining 133 patients who were untreated the recurrence rate was 20% by one month, 32% by three months, 40% by six months, 62% by one year, 69% by two years and 71% by three and four years.

4. Prognostic Factors

Prognostic factors were analysed in the 146 patients who presented following a first seizure by comparing the actuarial percentage of patients experiencing a recurrence, (see table 4:3). Patients who were under sixteen at the time of the first seizure had a higher recurrence rate (χ^2 = 5.8, d.f. = 1, p = 0.01) and patients with symptomatic seizures (χ^2=4.8, d.f.=1, p=0.02) also had a worse prognosis. Sex, neurological handicap, timing of seizures, the presence of a family history or EEG features were not of prognostic significance.

TABLE 4:3 PROGNOSTIC FACTORS FOR SEIZURE RECURRENCE IN 146 PATIENTS PRESENTING FOLLOWING A FIRST EVER SEIZURE. THE ACTUARIAL PERCENTAGE OF PATIENTS EXPERIENCING A SEIZURE RECURRENCE BY 1, 2 AND 4 YEARS OF FOLLOW-UP.

		Percent Recurrence at		
	Number of Patients	1yr	2yrs	4yrs
Sex				
Male	79	63	73	73
Female	67	54	62	66
Age at First Seizure				
=<16	41	75	79	-
>16	105	51	62	62
Aetiology				
Idiopatic	126	56	66	68
Symptomatic	20	76	77	-
Neurological Handicap				
Present	13	54	54	54
Absent	133	59	69	71
Family History of Seizures				
Present	12	50	67	67
Absent	134	60	68	70
Timing of Seizures				
Nocturnal	29	70	70	70
Diurnal	117	56	67	70
EEG Features				
Normal	49	60	72	72
Epileptiform	27	49	56	63
Non Specific	50	56	69	73
All patients	146	59	68	70

5. Precipitating Factors

Amongst the 146 patients, 35 were identified in whom an immediate precipitating event appeared to be of possible significance in causing the first seizure. Ten patients reported being uder some kind of stress at the time of the initial attack. This was a specific event in four patients: during a dental extraction, whilst having ears pierced, in the course of fitting an intra uterine device and shortly after being stung by a wasp. Nine patients reported a disturbence of sleep rhythms immediately before the first seizure, caused for example by overnight travel or shift work. Seven patients said they had consumed an unaccustomed amount of alcohol shortly before the seizure. This was often accompanied by lack of sleep, an all night party being the usual cause. Five patients had seizures precipitated by flashing lights of whom four showed photo-convulsive responses on the EEG. Four patients had seizures during the course of intercurrent illness, usually associated with fever. Amongst the total of 35 patients, 15(40%) experienced a seizure recurrence.

It can be difficult, even on the basis of a careful witnessed history, to distinguish an epileptic seizure from the convulsion that may follow a period of cerebral anoxia. Of the four patients in whom the initial attack immediately followed a painful or unpleasant event none had epileptic abnormalities on an EEG or subsequently developed unprovoked seizures. It is possible in these cases that the primary event was, in fact, syncope.

D. DISCUSSION

1. Comparison with Previous Prognostic Studies

The recurrence rate following a first seizure has been reported to vary widely from between 27 and 64% (see Table 1:8). There are a number of possible reasons for these differing results. Some authors, as in the present study, have included only those patients with tonic clonic seizures as these form the majority of patients who present following a single seizure (Todt et al,1985). Others series have contained a significant proportion with other seizure types (Hauser et al, 1982; Camfield et al, 1985; Annegers et al, 1986). As in all prognostic studies duration of follow-up is of crucial importance in determining the results. Todt et al (1985) only included relapses that occurred within one year of the first seizure. Many authors have failed to take account of variable follow-up and given only crude relapse rates rather than actuarial probabilities (Thomas, 1959; Saunders & Marshall, 1975; Cleland et al, 1981; Camfield et al, 1985). A further difficulty has been widely differing treatment policies with a number of more recent surveys showing that as many as two thirds of patients were given anticonvulsants following the first seizure (see Table 1:10).

Each of these factors have lead to difficulties in comparing the results of prognostic studies reported in the literature. An even more important source of error, however, has probably been the exclusion of patients who experience an early recurrence. In patients with established epilepsy, Gowers (1881) found that the second seizure followed the first within a month in one third of cases. (These findings have been confirmed in Chapter 5 of this thesis, see table 5:2.) In the present study the cumulative probability of recurrence was already 19% by one month and 30% by three months. If a significant period of time elapses, therefore, between the first seizure and entry into the study then patients will be excluded because they have already had a recurrence and are therefore ineligible for a study of patients with single seizures. The remaining patients, with what might be termed an isolated seizure (Cleland et al, 1981), will have a significantly better prognosis. Because the recurrence rate is highest in the months immediately following a seizure, patients who remain seizure free during this period will obviously have a better prognosis. In the present study 146 patients presented following a first seizure but 43(29%) had already developed epilepsy when seen in hospital a month after the initial event. In these patients the recurrence rate was considerably lower (see figure 4:1).

The influence of this form of patient selection on the results of prognostic studies of patients presenting with a single seizure is shown in Table 4:4. In the study by Cleland et al (1981) the interval between the first seizure and inclusion into the study was six weeks, which corresponded to the time taken for the patient to be seen in a neurology outpatients department. In this study the recurrence rate was 39%. A similar form of selection is likely to have taken place in two earlier studies (Thomas, 1959; Saunders & Marshall, 1975), both of which were based on patients attending EEG departments and where one third of patients subsequently developed epilepsy. In the most extensive study so far published, Hauser et al (1982) unfortunately failed to supply this crucial piece of information. Two hundred and fourteen patients with a single "unprovoked" seizure were followed for a median of 22 months and the recurrence rate was 27% by three years. It is likely, however, that a similar form of selection occurred as 435 patients who had experienced two or more seizures at the time of first diagnosis were excluded.

A similar consideration is the most likely explanation of the higher recurrence rate reported by more recent studies. Todt et al (1985) assessed the probability of seizure recurrence in 147 children who were seen in an EEG department within two weeks of a first ever tonic clonc seizure. Although follow-up information was only given for

TABLE 4:4 PROGNOSIS FOLLOWING A FIRST SEIZURE. THE INFLUENCE ON RECURRENCE RATE OF THE DELAY BETWEEN THE FIRST SEIZURE AND ENTRY INTO THE STUDY.

Author	Interval from first seizure to entry.	Recurrence Rate (%)
Saunders and Marshall, 1975	6 weeks	33
Cleland et al, 1981	6 weeks	39
Todt et al, 1985	2 weeks	59
Hopkins et al, 1988	8 weeks	22
	1 week	52
Present Study	1 day	71
	4 weeks	53

one year the reported recurrence rate was 59%. The importance that this form of patient selection may have on prognostic studies has recently been demonstrated by Hopkins et al (1988). In this study, in patients seen within one week of a first seizure the recurrence rate was 52% by 3 years of follow up. In those in whom a period of 8 weeks had elapsed before inclusion only 22% developed epilepsy.

2. Community Based Surveys

From the discussion considered above it is apparent that that the timing of the initial presentation and the subsequent referral patterns are likely to have an important impact on the results of prognostic studies of patients presenting with a single seizure. All except one of the studies summarised in Table 1:9 were hospital based and it is possible that a number of possible sources of bias could arise from this study design. In the present study patients were selected from a consecutive series of new referrals to a neurology outpatients department seen over a five year period. Those who presented following a first seizure were identified retrospectively. If, however, patients with more than one seizure are more likely to be referred to hospital this could lead to an over estimation of recurrence rates as the hospital population would be biased towards those with multiple attacks.

It is unlikely however that this was a major source of error. Available evidence suggests that between 80% and 95% of patients presenting to general practitioners in South East England with one or more seizures are referred to hospital for investigation (Hopkins & Scrambler, 1977; Goodridge & Shorvon, 1983). Furthermore, in this study patients selected on the basis of consecutive referrals to a hospital department appear to be broadly similar to those identified in community surveys. From a total of 214 patients seen over a five year period, 64 (30%) experienced only one attack. Goodridge & Shorvon (1983) retrospectively identified from general practice records patients who had at any time in their life experienced one or more seizures. In this study 19% experienced only a single attack. Comparable figures from the epidemiological surveys of Hauser & Kurland (1975) and Juul-Jensen & Foldspang (1983), were 17% and 24% respectively. These results are in broad agreemnt with those presented here, derived from patients consecutivley referred to a hospital department.

Another possible source of error is that the identification of patients who presented following a first seizure was, by necessity, retrospective. This was established either on the basis of an interview with the patient or from the referral letter from the general practitioner or casualty officer. It is posible, therefore, that a number of patients who presented with a single seizure were overlooked. If this

occurred in a significant proportion then this would lead to an underestimation of seizure recurrence.

A further factor that may influence recurrence rates is the proportion of patients who following the onset of seizures actually seek medical help after the very first attack. The impact that this may have on results of prognostic studies does not appear to have been considered previously. In the present study, out of a total of 214 patients seen as consecutive referrals to a neurology outpatients department, 146 (68%) were retrospectively identified as having presented following a first seizure. Although the recent onset of generalised seizures might be expected to be a dramatic event it appears that nearly one third of the patients had experienced two or more attacks before consulting a doctor. In the community based survey by Annegers et al (1985), which included patients with partial seizures, this occurred in one half of the patients who were identified using the records linkage system of the Mayo Clinic. It is possible that an initial noctural seizure might be more unlikely to go unnoticed. In other instances the importance might not be appreciated if an isolated episode of loss of consciousness occurred without the presence of a witness. Presumably the local availability and access to medical facilities could also be a factor. It is apparent, however, that if a greater proportion of patients sought help following the first attack then the

observed recurrence rate would be correspondingly higher. This issue could only be clarified with certainty by a prospective community based survey which identified patients at the onset of the disorder. If effective management strategies are to be developed then the proportion of cases who seek help early will need to be established.

3. Prognostic Factors

A number of prognostic factors were analysed by comparing the actuarial percentage of patients experiencing a seizure recurrence. Patients with a symptomatic first seizure had a higher recurrence rate, in keeping with the findings of most other reports (Hauser et al, 1982; Camfield et al, 1985; Annegers et al, 1986). Age at first seizure was also an important prognostic indicator but sex of the patient, the presence of neurological deficits, EEG features, the timing of seizures and the presence or absence of a family history of epilepsy did not significantly affect outcome.

In assessing prognostic factors it is important to emphasise that patients with single seizures are a selected group and differ from those with epilepsy in a number of important respects. Patients with partial seizures are largely excluded because the majority have experienced multiple attacks when first seen. Similarly there is likely to be a lower incidence of symptomatic seizures; in the present

study, amongst patients presenting with single seizures, the incidence was 14%, compared to 33% for those with established epilepsy considered in the previous chapter. These two features, which are amongst the most important prognostic factors in patients with epilepsy (see Chapter 3), will be selected out in series of patients with single seizures.

In the present study patients who were aged 16 or less had a recurrence rate of 79% compared with adults of whom 62% developed epilepsy. These findings were based on patients referred to an adult neurology outpatients department, over two-thirds of cases being aged over 16 years. It is possible that general practitioners and casualty officers might have been more likely to refer children to an adult clinic if they had epilepsy rather than just a single seizure. Further examination of the data did not suggest any such source of bias. The proportion of patients with single or multiple seizures for all the 214 patients was similar for both the adult and paediatric populations. Patients who were aged 16 or less at the time of the first seizure did not have a higher incidence of symptomatic epilepsy or neurological handicaps. Annegers et al (1986) found that age of onset did not significantly affect prognosis following a first seizure. The age structure in this study was curious with over half the patents apparently aged 55 or over suggesting that children were, for some

reason, largely excluded. Three childhood studies by Hirtz et al (1984), Todt et al (1985) and Camfield et al (1985) have stated that children are more likely to experience a recurrence following a first seizure. These claims, however, are also difficult to intrepret. Earlier prognostic studies, all of them based on adults, showed recurrence rates of the order of 30% (Thomas, 1959; Saunders & Marshall, 1975, Cleland et al, 1981; Hauser et al, 1982). These results however are not strictly comparable to those of Todt et al (1985) for the reasons of patient selection discussed above. Similarly the children identified by Hirtz et al (1984) came from a population study and all such studies, whether in adults or children, have shown higher recurrence rates.

The features of the initial EEG were not of value in predicting prognosis but this must be interpreted with caution as a number of patients did not have this investigation performed. Again there is little agreement in the literature on the value of this procedure in assessing recurrence following a first seizure. The most carefully documentated study in this respect is that by Camfield et al (1985), based on a paediatric population. The presence of either slow wave abnormalities or generalised spike and wave had no effect on outcome. The prognosis was worse in a sub group of patients with focal epileptiform features, 68% experiencing the recurrence as opposed to 52% for the remaining patients. Annegers et al (1986) found that none

of these features when considered separately affected prognosis whilst Hauser et al (1982) found a higher recurrence rate only amongst a small group of patients with generalised spike and wave. Hopkins et al (1988) has recently reported that the EEG is of little value in predicting prognosis.

E. SUMMARY

1. The prognosis following a first seizure has been assessed in a series of 214 patients who were consecutively referred to a neurology outpatients department over a 5 year period because of recent onset of one or more tonic clonic seizures.

2. After a median follow up of 21 months, 150 patients (70%) had experienced recurrent seizures and 64 patients (30%) had had only a single attack. Patients who developed epilepsy were more likely to have symptomatic seizures and to be under the age of 16, but otherwise the two groups did not appear to differ in any major respect.

3. One hundred and forty six patients were retrospectively identified who had presented to medical attention within a median interval of 1 day following a first tonic clonic seizure. Thirteen patients were treated following the first seizure. The cumulative probability of seizure recurrence was 19% by 1 month, 30% by 3 months, 44% by 6 months, 60% by 1 year and 71% by 3 and 4 years.

4. Forty-three patients had relapsed by the time of first attendance at the neurology outpatients department. Amongst the remaining 103 patients the cumulative probability of seizure recurrence was 10% by 3 months, 24% by 6 months, 42%

by 1 year, 54% by 2 years and 57% by 3 years.

5. Patients who were aged 16 years or less at the time of the first seizure and those with symptomatic seizures had a significantly higher recurrence rate. Sex, neurological handicap, timing of seizures, the presence of a family history or EEG features were not of prognostic signficance.

CONCLUSIONS

Following a first seizure the majority of patients are likely to develop epilepsy. The second seizure follows the first in rapid succession and most patients experience a recurrence within one year. Patients with symptomatic seizures are more likely to experience a recurrence but there is little agreement on the nature of other adverse prognostic factors.

Many prognostic studies of patients presenting with a single seizure have considerably underestimated recurrence rates by excluding patients who experience an early recurrence. The results presented here, based on consecutive referrals to a neurology outpatients department, are in broad agreement with those from epidemiological surveys which have shown that seizures are likely to be recurrent in as many as 60% to 80% of cases.

CHAPTER FIVE

INTERVALS BETWEEN UNTREATED TONIC CLONIC SEIZURES IN PATIENTS WITH NEWLY DIAGNOSED EPILEPSY.

A. INTRODUCTION

Remarkably little is known about the patterns of seizure recurrence at the onset of epilepsy. Apart from some observations in the historical literature (Gowers, 1881) there appears to have been no study of this aspect of the prognosis of epilepsy in either treated or untreated patients.

In this Chapter an analysis of patterns of seizure recurrence prior to the onset of treatment in a series of 183 patients with tonic clonic seizures will be presented. The data has been analysed with the following aims:

i. To analyse the intervals between the first and second untreated seizures in patients with epilepsy

ii. To assess the influence of subsequent seizures on inter-seizure intervals

iii. To assess the impact of the early patterns of seizure recurrence on the subsequent prognosis of epilepsy.

B. PATIENTS AND METHODS

The patients considered for inclusion into the study were all referrals to the the Neurology Outpatients Department at Kings College Hospital with newly diagnosed previously untreated epilepsy. Between 1978 and 1984 a total of 388 patients were seen. Of these, 127 experienced partial seizures without secondary generalisation, petit mal or myoclonic seizures and the remaining 281 patients had tonic clonic seizures.

As was described in Chapter two, during this period the Department had a major interest in identifying patients with newly diagnosed epilepsy for inclusion into trials of monotherapy using the major established anticonvulsant drugs. Both adults and children were recruited for the trials. Patients with a progressive neurological disorder which was apparent at the time of first referral and those in whom seizures were caused by an acute metabolic or neurological disturbance, drugs, alcohol or fever were excluded.

Details of the patients' seizure history, past medical, social and psychiatric history and the results of the examination and pretreatment investigations were entered onto a proforma (Appendix 1). Patients were initiated on treatment if they had experienced at least two tonic

clonic seizures within the space of one year or a sufficient number of partial seizures to warrant medication, in accordance with standard clinical practice.

In assessing the early patterns of seizure recurrence only those patients in whom the dates of individual seizures could be accurately ascertained were studied. This information was recorded at the time of the first attendance at the Neurology Outpatients Department. The letter from the general practitioner or casualty officer was often of considerable use as the date of initial presentation and the timing of subsequent seizures had often been recorded by the referring doctor. It became apparent that patients who had experienced partial seizures without secondary generalisation, petit mal or myoclonus had almost invariably had a large number of attacks that could not be accurately dated. Although the intervals between individual seizures were known in a small number of patients with complex partial seizures, these were excluded in order that a uniform series of patients with tonic clonic seizures could be studied.

The first tonic clonic seizure was defined as the first ever afebrile tonic clonic seizure. Patients with a past history of other seizure types, such as petit mal or partial seizures that had previously gone unrecognised were not included. Patients who developed another seizure

type prior to treatment were also excluded. The intervals between individual seizures were measured in weeks and the difference between consecutive intervals were assessed using parametric analysis. The influence of the early patterns of seizure recurrence on the subsequent prognosis was analysed by measuring the actuarial percentage of patients remaining seizure free or achieving a one year remission on treatment.

C RESULTS

1. Patient Characteristics

The patients considered for inclusion into the study were all new referrals to the Neurology Outpatients Department with newly diagnosed previously untreated epilepsy. Between 1978 and 1984 a total of 281 patients were seen who had experienced two or more untreated tonic clonic seizures. Amongst these patients it was possible to accurately measure the intervals between individual tonic clonic seizures in 183, and these patients form the basis of this study (see Appendix 6). The characteristics of these patients and the 98 patients in whom the intervals were unknown are shown in Table 5:1. Ninety-nine patients (54%) were male and 84 (46%) were female. Twenty patients (11%) had symptomatic epilepsy and 18 (10%) had associated neurological handicaps. The median age at first seizure was 17 years, range 2 to 65. One hundred and one (55%) had experienced 2 pre-treatment seizures, 53 (29%) had 3, 18 (10%) had 4 and 11 (6%) had 5 or more.

There were 98 patients in whom the dates of individual tonic clonic seizures were unknown. Amongst these patients the pre-treatment interval and total number of seizures could be ascertained in 76. A comparison of the two groups of patients is shown in Table 5:1. The

TABLE 5:1 CHARACTERISTICS OF 281 PATIENTS WITH TWO OR MORE UNTREATED TONIC CLONIC SEIZURES. A COMPARISON OF PATIENTS WITH KNOWN (N=183) AND THOSE WITH UNKNOWN (N=98) SEIZURE INTERVALS

	Patients With Known Intervals N (%)	Patients With Unknown Interval N (%)
Male	99(54)	46 (47)
Female	84(46)	52 (53)
Symptomatic Epilepsy	20(11)	16 (16)
Neurological Handicap	18(10)	12 (12)
Median Age at First Seizure, Years (range)	17(2-65)	23 (1-82)
Pretreatment Seizure Number		
Two	101(55)	7 (9)
Three	53 (29)	16 (22)
Four	18 (10)	18 (10)
Five or more	11 (6)	35 (48)
Median Pretreatment Interval, Months (range)	6 (1-132)	9 (1-276)
Pre-treatment Seizure Frequency (seizures per month)	0.5	0.85
Totals	186(100)	98 (100)

pre-treatment seizure frequency was 0.5 seizures per month in the 183 patients with known seizure intervals compared with 0.85 for those in whom the dates of individuals were unknown. The patients with unknown seizure intervals had experienced a larger number of attacks occurring over a longer period of time. Amongst the patients with unknown seizure intervals nearly one half had experienced 5 or more seizures, compared to only 10% for the other 183 who were entered into the study.

2. Intervals Between the First and Second Seizures

An analysis of the intervals between the first and second seizures in the 183 patients is shown in Table 5:2. In 56 patients (31%) the interval was equal to or less than one month. In 19 patients (10%) it was between one and two months and in a further 18 (10%) between two and three months. In 66 patients (36%) it was greater than three months but equal to or less than one year. The interval between the first and second seizures exceeded one year in 24 patients (13%).

3. Intervals Between Subsequent Seizures

The median interval between successive untreated tonic clonic seizures decreased with each seizure that occurred (Table 5:3). The median interval between

TABLE 5:2 INTERVALS BETWEEN THE FIRST AND SECOND UNTREATED TONIC CLONIC SEIZURES IN 183 PATIENTS WITH EPILEPSY

Interval Beteen First Two Seizures	N	(%)
Equal to or less than 1 month	56	(31)
Between 1 and 2 months	19	(10)
Between 2 and 3 months	18	(10)
Between 3 and 12 months	66	(36)
Greater than one year	24	(13)
Between 1 and 2 years	14	(8)
Between 2 and 3 years	4	(2)
Greater than 3 years	6	(3)
Totals	183	(100)

TABLE 5:3 MEDIAN INTERVALS BETWEEN CONSECUTIVE UNTREATED TONIC CLONIC SEIZURES IN 183 PATIENTS WITH EPILEPSY

	Pretreatment Seizure Number				
	All (N=183)	2 (N=101)	3 (N=53)	4 (N=18)	5 (N=11)
	Median Inter-seizure Interval weeks(25th to 75th centiles)				
From 1st to 2nd seizure	12(4-28)	12(4-25)	12(4-44)	22(4-36)	24(4-42)
From 2nd to 3rd seizure	8 (4-16)	-	8 (4-16)	16(4-40)	4 (4-12)
From 3rd to 4th seizure	4 (2-23)	-	-	6 (2-24)	4 (2-20)
From 4th to 5th seizure	3 (2-4)	-	-	-	3 (2-4)

first and second seizure was 12 weeks, between the second and third it was 8 weeks , between the third and fourth it was 4 weeks and between the fourth and fifth it was 3 weeks. When patients with three, four or five pretreatment seizures were considered separately a similar trend was seen. In 53 patients who experienced three seizures the interval fell from 12 weeks between the first and second seizure to 8 weeks between the second and third. In patients with 4 pretreatment seizures it fell from 22 to 16 to 6 weeks with each successive seizure. In 11 patients with 5 pretreatment seizures the interval between the first and second was 24 weeks, between the second and third it was 4 weeks, between the third and fourth it was 4 weeks and between the fourth and fifth it was 3 weeks.

A parametric analysis of the difference in successive seizure intervals was undertaken. Eighty-two patients experienced at least three untreated seizures; in these patients the interval from the first to the second seizure was on average 18.1 weeks longer than the interval between the second and third, with 95% confidence levels at 5.4 and 30.7 weeks. The mean difference between the second and third intervals was 4.1 weeks and between the third and fourth intervals was 22.5 weeks. The decrease between these seizure intervals was not statisticaly significant.

The majority of patients were treated following the second or third seizure (table 5:1). However it was possible to compare the interval between any two seizures with that between the subsequent two on 122 occasions (Table 5:4); the interval between the first and second seizure with that between the second and third in 82 patients; the second to the third with the third to the fourth in 29 patients and third to the fourth with fourth to the fifth in 11 patients. In 71 instances (58%) the interval decreased, in 25 (21%) it remained the same and in 26(21%) it increased.

4. The Influence of the Interval between the First and Second Seizures on the Subsequent Prognosis on Treatment.

The influence of the interval between the first and second seizures on the subsequent prognosis on treatment was assessed for three groups of patients: those in whom the interval between the first two seizures was equal or less than 4 weeks (N=56), those in whom it was between 5 and 24 weeks (N=72) and the remaining 55 patients where it exceeded 24 weeks (N=55). The outcome on treatment for the last two groups of patients was very similar and only the data relating to those with shorter interseizure intervals are given in the Table and Figures below. The prognosis was analysed by comparing the actuarial percentage of

TABLE 5:4 AN ANALYSIS OF 122 SUCCESSIVE SEIZURE INTERVALS IN PATIENTS WITH UNTREATED TONIC CLONIC SEIZURES. THE PROPORTION OF CASES IN WHICH THE SEIZURE INTERVAL DECREASED, REMAINED THE SAME OR INCREASED

	Successive Seizure Intervals			
	1st to 2nd v. 2nd to 3rd N (%)	2nd to 3rd v. 3rd to 4th N (%)	3rd to 4th v. 4th to 5th N (%)	Totals N (%)
Decreased	48(59)	17(59)	6(55)	71(58)
The same	16(19)	5(17)	4(36)	25(21)
Increased	18(22)	7(24)	1(9)	26(21)
All	82(100)	29(100)	11(100)	122(100)

patients remaining seizure free and the cumulative probability of achieving a one year remission on treatment.

Amongst the 56 patients in whom the initial interval between the first and second seizures was equal to or less than four weeks, five were untreated and in a further eight follow up details on treatment were not available. In 72 patients the interval between the first and second seizure was between 5 and 24 weeks. In this group five patients were untreated and no follow up was available in seven.

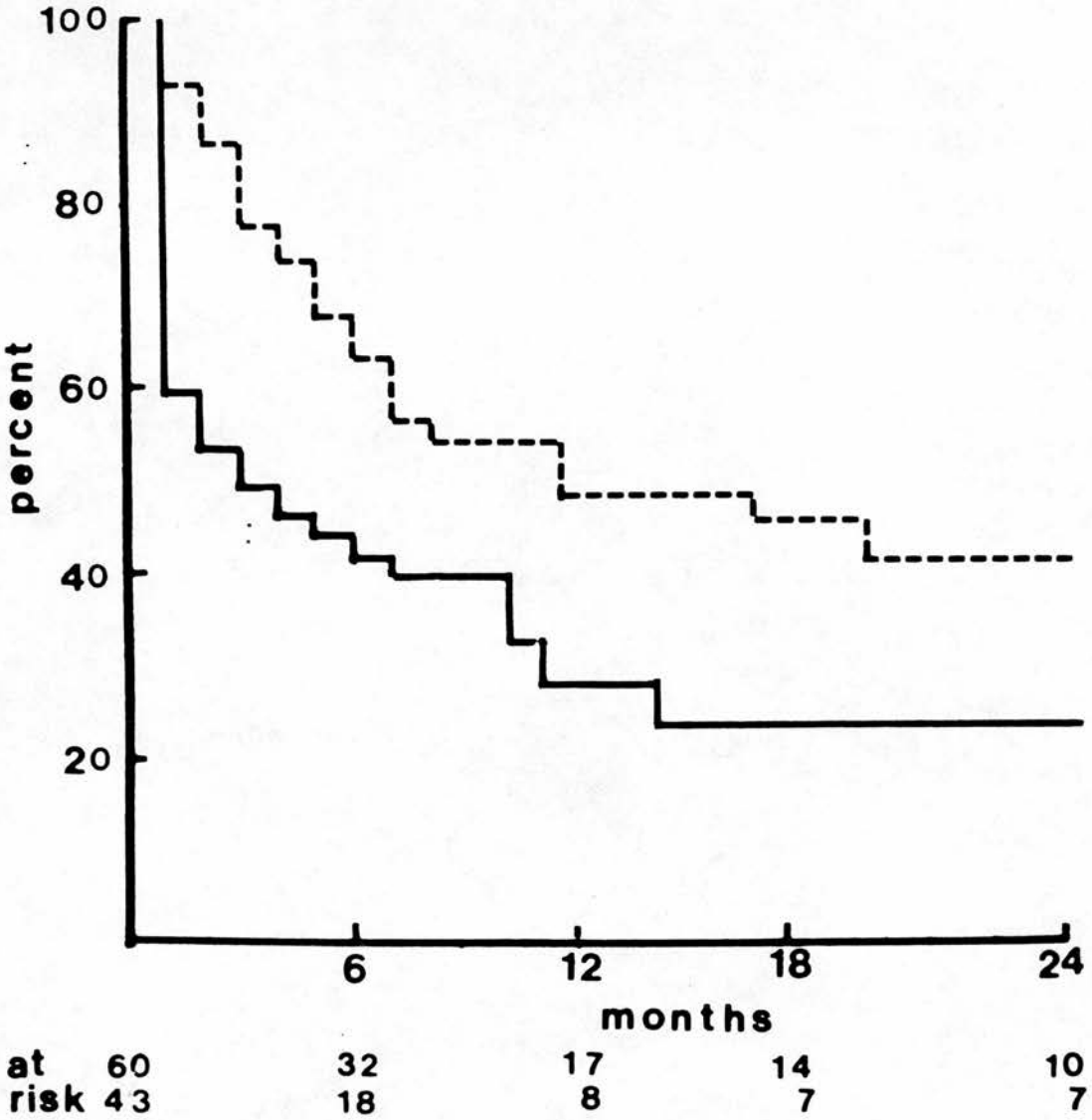
The clinical characteristics of the two groups are summarised in Table 5:5. There was no difference in the total pretreatment seizure numbers. In patients with a short initial interseizure interval the median pretreatment period was 2.5 months and the seizure frequency was 0.97 seizures per month. In the patients with a long interseizure interval the corresponding figures were 6 months and 0.31 seizures per month. The median follow up from the start of treatment was 21 and 13 months respectively.

The probability of remaining seizure free from the start of treatment for the two groups is shown in Figure 5:1. In patients in whom the interval between the first two

TABLE 5:5 THE INFLUENCE OF THE INTERVAL BETWEEN THE FIRST AND SECOND SEIZURES ON THE SUBSEQUENT PROGNOSIS : A COMPARISON OF THE CLINICAL CHARACTERISTICS OF THOSE WITH SHORT AND LONG INTER SEIZURE INTERVAL

	Intervals Between 1st and 2nd Seizure	
	= or less than 4 weeks (N=56)	between 5 and 24 weeks (N=72)
	N (%)	N (%)
Male	30 (54)	46 (64)
Female	26 (46)	28 (36)
Symptomatic Epilepsy	7 (13)	7 (10)
Neurological Handicap	5 (9)	10 (14)
Median Age at First Seizure, Years (Range)	19 (4-65)	15 (3-66)
Pretreatment Seizure Number		
Two	27 (48)	42 (58)
Three	16 (29)	21 (29)
Four or more	13 (23)	9 (13)
Median Pretreatment Interval, Months (range)	2.5 (1-11)	6 (5-57)
Pre-treatment Seizure Frequency (seizures per month)	0.97	0.31
Totals	56 (100)	72 (100)

FIGURE 5:1 THE INFLUENCE OF THE INTERVAL BETWEEN THE FIRST AND SECOND SEIZURES ON THE ACTUARIAL PERCENTAGE OF PATIENTS REMAINING SEIZURE-FREE ON TREATMENT



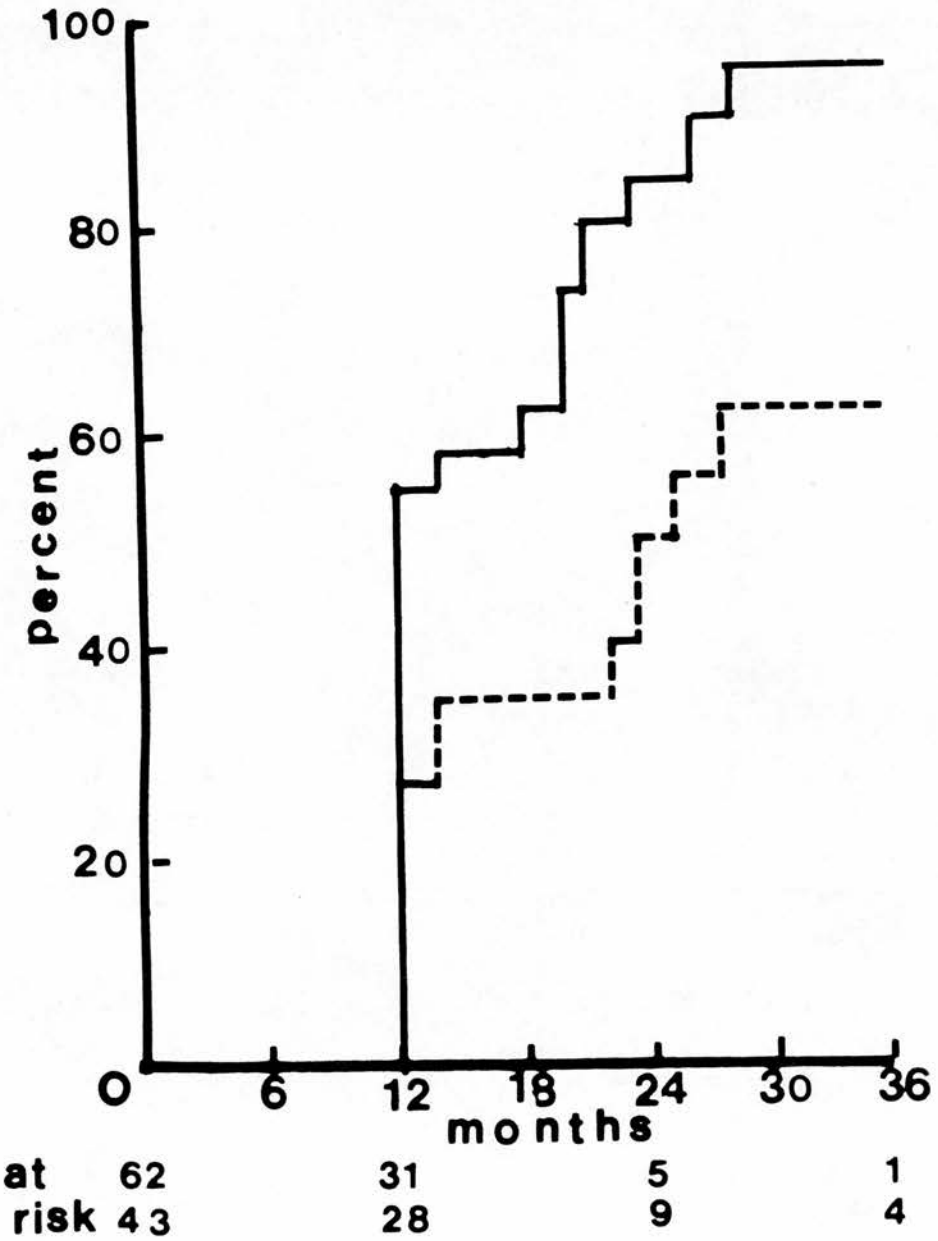
Broken lines = Patients in whom the interval between the first two seizures was greater than one month.

Solid lines = Patients in whom the interval between the first two seizures was equal to or less than one month

seizures was between one and four months the cumulative probability of subsequently remaining seizure-free on treatment was 50% by 3 months, 42% by 6 months, 29% by 1 year and 25% by 2 years. The corresponding figures for patients with a long initial interseizure interval were 78%, 64%, 46% and 38% (χ^2 = 5.4. d.f.=1, p= 0.02).

Patients in whom the second seizure followed the first within a month were also less likely to remit on treatment. Amongst these patients the cumulative probability of achieving a 1 year remission on treatment was 27% by 1 year, 35% by 18 months, 50% by 2 years and 61% by 3 years (figure 5:2). In patients in whom the interval between the first two seizures was between 4 and 24 weeks, the remission rates were 55% by 1 year, 62% by 18 months, 84% by 2 years, and 94% by 3 years (χ^2 = 4.3, d.f=1, p= 0.05).

FIGURE 5:2 THE INFLUENCE OF THE INTERVAL BETWEEN THE FIRST AND SECOND SEIZURES ON THE ACTUARIAL PERCENTAGE OF PATIENTS REMAINING SEIZURE-FREE FOR ONE YEAR ON TREATMENT



-Solid lines = Patients in whom the interval between the first two seizures was equal to or less than one month
-Broken lines = Patients in whom the interval between the first two seizures was greater than one month

D. DISCUSSION

It is curious that amongst the considerable volume of literature on the prognosis of patients with epilepsy, there has been virtually no study of the patterns of seizure recurrence at the onset of the disorder. An understanding of this neglected area is of considerable importance. According to the figures of Hauser and Kurland (1975), at least 5% of the population can be expected to experience at least one afebrile seizure at some time during their life. A lack of clear prognostic data has led to continuing uncertainty about the probability of seizure recurrence, little information on the nature of adverse prognostic factors and widely differing management policies (Hauser, 1986; Elwes & Reynolds, 1988).

An analysis of the intervals between the first and second seizures in 183 cases of epilepsy has been presented in Table 5:2. The second seizure followed the first within a month in one third of cases, by three months in half of the patients and within a year in over four fifths. In patients with established epilepsy therefore the second seizure follows the first in rapid sucession. It was argued at some length in the previous Chapter that many prognostic studies in patients presenting with a single seizure have failed to take account of this and excluded a significant proportion of cases who experienced an early recurrence.

Although over half the patients were treated following the second seizure, it was possible to observe the intervals between multiple untreated seizures in a number of cases. Fifty-three patients had experienced 3 pretreatment seizures, 18 had had 4, and a further 11 had 5 or more seizures before receiving medication. When four or more seizures had occurred the median interval between attacks was of the order of one month (see Table 5:3). The only comparable data is to be found in the historical literature. Gowers (1881) reported that in 680 cases of "confirmed" epilepsy, the majority untreated, the interval between seizures was of the order of one month in 80% of cases. Herpin and Reynolds, writing prior to the widespread introduction of bromides quoted similar results (see Paskind & Brown (1939) for a review of the early literature).

1. Decreasing Seizure Intervals

A striking observation to arise from this study was the tendency for the intervals between successive untreated seizures to decrease with each seizure that occurred. The median interval between the first and second attack was 12 weeks whilst between subsequent seizures it decreased progressively to 8, 4 and 3 weeks. A similar trend was seen when patients with 3, 4 or 5 seizures were considered separately. It was possible to observe successive seizure

intervals on 122 occasions. In three-fifths of cases the interval decreased, in one-fifth it remained the same, and in the remaining fifth it increased.

There are, however, two possible sources of bias that must lead to a cautious interpretation of these results. There were 98 patients excluded from the analysis because the precise intervals between untreated seizures could not be accurately ascertained. These tended to be patients who had experienced a much larger number of attacks with a higher seizure frequency, of the order of 0.8 seizures per month. In comparison the seizure frequency for the 183 patients who formed the basis of the analysis was 0.5 per month. Because the group who were selected for the study had a lower seizure frequency, they might appear on follow up to have an increasing seizure frequency because of regression towards the mean. This is a well described occurrence in many biological systems where some form of bias is introduced into the initial selection of the sample (James, 1973). A second difficulty with the results is that the timing of the initiation of treatment was not made on a randomised basis. For example following initial presentation a period of one month might elapse before treatment was started. This would roughly correspond to the time when investigations were being undertaken. A number of patients might experience a relapse during this period and therefore the sample would

be biased towards those in whom subsequent attacks occurred in rapid succession.

It is difficult to be certain to what extent both of these considerations could have affected the results. In patients with 2 or 3 pretreatment seizures, the median interval between the first and second attack was equal for both groups. This does not suggest that in these patients (who formed over four-fifths of all those studied) that any important selection bias had ocurred. There is no doubt on the basis of clinical observation that there were a number of striking cases in whom it was possible to document the occurrence of decreasing seizure intervals in some detail. This is well illustrated by the following case histories.

1. C.P., a 12 year old girl was initially seen in the department in December 1981 having been referred because of a single seizure. Her birth and early development had been normal and her past history was blameless. There was no family history of epilepsy. She was of high intelligence and neurological examination revealed no abnormality. A C.T. brain scan was normal and the EEG showed generalised spike and wave evoked by photic stimulation. Treatment was withheld and she was given a follow up appointment but her parents failed to attend. She was readmitted to hospital on 7.1.1983 in status epilepticus having experienced 7 seizures without regaining consciousness. Following

intravenous diazepam her seizure were controlled and she fortunately made a full recovery and has subsequently responded well to treatment with sodium valproate. It transpired that for the previous year her parents had taken her to a herbalist who instructed them to keep a diary of all seizures that occurred. The unfortunate child experienced multiple seizures extending over the period of a year. Although the intervals between the initial seizures increased she subsequently had clusters of attacks with decreasing intervals between the episodes culminating in status epilepticus one year after the initial seizure. There is little doubt that if effective treatment had been instituted immediately she would have remained largely seizure-free.

ii. D.M., a 48 year old man developed seizures secondary to an arterio-venus malformation which came to light following a subarachnoid haemorrhage in 1967. His first seizure occurred seven years after the haemorrhage and the second attack five years later. According to his wife the next seizure occurred after two years and successively at intervals of 18, 6, 2.5, 2, 2, and 1.5 months at which time he was treated with diazepam. Following this the intervals fluctuated and occurred at intervals of around 3 months. He was subsequently given carbamazepine and has achieved a satisfactory remission of seizures.

It is, of course, uncertain what proportion of cases would have a similar outcome if treatment were witheld. Turner (1907) in his book on Epilepsy described the phenomenon of decreasing intervals between multiple untreated seizures in some detail. Gowers (1881) stated that seizures were self propagating, each attack predisposing to the next and that spontaneous remission of the disorder was exceptionally rare. For the reasons discussed above the results presented here must be treated with caution as there is likely to be a major source of bias introduced by inescapable ethical and practical considerations. However the findings are in agreement with Gowers' hypothesis and do not suggest that many patients would be likely to remit spontaneously, at least at the onset of epilepsy. Further studies are needed to examine the initial patterns of seizure recurrence in epilepsy. It would be of considerable interest to document the impact of treatment on the intervals between seizures, particularly if the decision to start or withold treatment was made on a randomised basis. The possibility of undertaking such a trial will be discussed in greater detail in the next Chapter.

2. The Early Patterns of Seizure Recurrence Determine the Long Term Prognosis of Epilepsy.

A related question that has received little attention in the literature is the influence of the early patterns of seizure recurrence on the subsequent prognosis of epilepsy. In Chapter 3 it was found that pretreatment tonic clonic seizure frequency was the single most important factor determining the probability of remaining completely seizure free from the start of treatment (see figure 3:2). Similarly patients with a high initial seizure frequency were less likely to achieve a prolonged period of seizure control (see Table 3:3). A number of other authors have reported that a high pre-treatment seizure frequency is a poor prognostic sign (Strobos, 1959; Kuhl et al, 1967; Okuma & Kumashiro, 1981; Schmidt et al, 1983). These results, however, are open to a number of difficulties in interpretation as all except Schmidt et al (1983) did not distinguish between different seizure types. It is important that patients with generalised convulsions be considered separately from those with partial seizures. In the latter group, who are known to have a poor prognosis, seizures almost always occur in greater numbers, and often at a higher frecqency.

In the present Chapter the influence of the interval between the first and second tonic clonic seizure on the

subsequent prognosis was studied. This is a more precise measurement than seizure frequency as the latter will depend to some extent on the timing of initiation of treatment. In patients in whom the interval between the first and second seizures was equal to or less than a month 25% remained completely seizure free on treatment. The comparable figure for patients in whom the interval was between 4 and 24 weeks was 38%. Similarly in patients with a short initial interseizure interval 61% remitted on treatment compared to 94% for those patients with a longer interval. This is an important observation and suggests that the initial seizure interval may determine the duration of time for which epilepsy is likely to remain active. The possibility arises that early treatment following the first seizure might delay the occurrence of the second attack and improve the subsequent prognosis of epilepsy.

E. SUMMARY

1. The intervals between untreated tonic clonic seizures have been analysed in a consecutive series of 183 patients with newly diagnosed epilepsy. One hundred and one patients had experienced 2 pretreatment seizures, 53 had 3, 18 had 4 and a further 11 had had 5 or more attacks before treatment.

2. The second seizure followed the first within a month in 30% of cases and within 3 months in 51%. The interval between the first two seizures exceeded 1 year in 13%.

3. The median interval between the first two seizures was 12 weeks, between the second and third it was 8 weeks, 4 weeks between the third and fourth and 3 weeks between the fourth and fifth. When patients with 3, 4 or 5 or more seizures were analysed separately a similar decreasing interval between successive attacks was seen. Using parametric analysis the decrease between the first three seizures was significant at the 95% level. It was possible to observe intervals between successive seizures on 122 occasions. In three-fifths of cases the interval decreased, in one-fifth it remained the same and in one-fifth it increased.

5. The influence of the interval between the first and second seizure on the subsequent prognosis on treatment was examined. In patients in whom the second seizure followed the first within a month 25% remained seizure free at 2 years of follow up. In those in whom the first interseizure interval was between 5 and 24 weeks 38% remained seizure free. Amongst patients with a shorter initial seizure interval 61% achieved one year remission by 3 years of follow up whilst those with a longer interval 94% achieved remission.

CONCLUSIONS

In established epilepsy the second tonic clonic seizure follows the first in rapid succession, within a month in one third of cases and within three months in one half of patients. The interval between successive untreated seizures appears to decrease with each seizure that occurs. Patients in whom the second seizure follows the first within four weeks have a signficantly worse prognosis on treatment. These findings suggest that the early patterns of seizure recurrence are of considerable importance in determining the subsequent prognosis of epilepsy. Further prospective studies are needed to clarrify these issues and to determine the effects of early and delayed tretment on the long term prognosis of epilepsy.

CHAPTER SIX

GENERAL DISCUSSION

A. DIFFERING CONCEPTS OF PROGNOSIS IN EPILEPSY

The prognosis of patients with epilepsy has always been a subject of considerable controversy. The literature, both historical and modern, is full of conflicting statements. The Ancients felt that prognosis in epilepsy was generally gloomy. Epilepsy dating from birth was thought to be incurable and if it started after the age of 25 years, it usually lasted until death. Epilepsy that began in old age was usually fatal. However it was recognised, even in the Hippocratic writings, that the prognosis might be better in childhood and that in general it was important to treat the disease before it became chronic (Temkin, 1971).

Similarly, many writers in the Nineteenth Century also felt that prognosis was poor. Reynolds, Delasuive, Esquirol, Heberden and Fere all emphasised the poor response to treatment, although as Temkin (1971) has pointed out, many of these authors based their experience on institutionalised patients. In contrast to these views, Herpin's work caused considerable controversy when he claimed to cure half of his patients and ameliorate seizures in another one

quarter using zinc oxide (see page 78).

During the second half of the 19th century a major advance in the treatment of epilepsy occurred. The credit for the introduction of bromides has been given to Sir Charles Lowcock following a remark made at a meeting of the Royal Medical and Chirurgical Society in 1857 (Sieveking, 1857). Within four years Wilks (1861) stated that the drug was used in all new cases of epilepsy and that it was "singularly efficacious". Gowers (1881) thought that the prognosis of epilepsy had been "materialy changed" by their introduction and they were effective in cases which had previously been considered most unpromising (see page 36). As late as 1953 Livingston claimed that they were highly effective in childhood epilepsy. A number of carefully documented clinical trials are available in the 20th century literature comparing their efficacy favourably with currently available drugs (Pollock, 1938. Arieff, 1951. Livingston & Pearson 1953.)

Although the subsequent introduction of phenobarbitone in 1912 (Hauptmann, 1912) and phenytoin in 1938 (Merritt & Putnam, 1938) were important advances, largely because these drugs were felt to be less toxic, there is surprisingly little evidence that they were any more effective than bromides in controlling seizures. Following their widespread usage, the opinions of many authoritative

authors in the first half of this century, such as Gibbs (1947), Livingston (1958) and Lennox & Lennox (1960) was that as many as three quarters of patients were either improved or completely controlled on medication.

It might have been hoped that with the widespsread usage of drugs of undoubted efficacy clear evidence as to their beneficial effects on the prognosis of epilepsy would have been established. It is curious, however, that Rodin (1968) in an authoritative review written a century after the introduction of bromides, could find little evidence that this was indeed the case. He criticised the opinions of previous authors because their observations were based on inadequate follow up of patients and that furthermore the great majority has failed to define clearly what constituted control of seizures. He found that all the prognostic studies that overcame these methodological problems showed that at most only one third of patients could expect to be controlled for a period of one year or more (see Table 1:11). Furthermore because of the tendency of the disease to relapse epilepsy was likely to be a chronic disorder in 80% of cases.

Rodins' work, and the prognostic studies on which he based his authoritative and widely quoted review are open to a number of important criticisms. As was discussed in Chapter 3 differing methods of classification, retrospect-

ive analysis and poor documentation of treatment methods have led to difficulties in interpretation of the results. The single most important criticism, however, has been patient selection. Because of the highly variable outcome in epilepsy selection of patients is of crucial importance in determining the results of prognostic studies. Patients with intractable seizure disorders are likely to accumulate in specialised neurology or epilepsy clinics. Follow up studies based on a cross sectional selection of patients attending such clinics is likely to give an unduly gloomy view of prognosis. In some of the studies quoted by Rodin (see Table 3:5) the mean duration of epilepsy prior to entry was greater than ten years. Unfortunately not all authors have clearly stated the methods of patient selection but there is little doubt that patients with chronic epilepsy have been strongly over represented.

B. THE PROGNOSIS FOR SEIZURE CONTROL IN NEWLY DIAGNOSED EPILEPSY

There is almost a complete dearth in the literature of prognostic studies that have examined the initial response to treatment and the prognosis during the early years of the disorder. Only one study has commented upon initial remission and relapse rates, and this was undertaken with special reference to traffic security (Kuhl et al, 1967). Prognostic studies based on the follow-up of consecutive new cases are, of course, harder to undertake. Unless a multicentre design is used patient recruitment takes a prolonged period of time. Furthermore there are difficulties in maintaining prolonged follow-up. Many patients with de novo onset of seizures are referred to hospital primarily for diagnosis and investigation. A considerable number subsequently default from follow up or are discharged back to the care of their family practitioner.

The prognostic study described in Chapter 3 was unique in that patients were identified as a group from the time of diagnosis. Follow up was prospective for periods of almost a decade. Not only was a detailed record kept of the timing and number of seizures experienced but a consistent policy of treatment was maintained throughout the period of follow up. Patients were treated with monotherapy with

widespread use of anticonvulsant level monitoring to assess optimum treatment and poor compliance with medication. A number of important conclusions arise from this work which will be considered below.

1. First Seizure Recurrence on Treatment

The majority of patients with newly diagnosed epilepsy experience at least one further seizure on treatment. Out of the 106 patients considered in Chapter 3, 80 experienced a further seizure on treatment, most occurring within the first year of follow up. On the basis of actuarial probabilities (see Figure 3:1) 60% could be expected to have a recurrence during the first year of treatment and a further 19% during the next seven years of follow up.

A number of anticonvulsant trials in newly diagnosed epilepsy have been published in recent years (see Table 1:4). These have all been analysed by examining the proportion of patients remaining seizure free from the start of treatment. Those with short periods of follow up (Strandjord & Johannessen, 1980; Feely et al, 1982) have shown that approximately 20% of patients experience a seizure recurrence. In the study by Turnbull et al (1982), where all the patients were followed for at least one year, 42% experienced further seizures. In the Veterans

Administration Trial (Mattson et al, 1985) patients were followed for periods of up to six years and the relapse rates reported were very similar to those given here. These findings emphasise that in analysing outcome in newly diagnosed epilepsy duration of follow up is of crucial importance in determining the results. When there is variable follow up actuarial probabilities rather than crude relapse rates should be used.

2. Remission and Relapse Rates in Newly Daignosed Epilepsy

Although most patients experienced at least one further seizure after starting treatment the subsequent prognosis for seizure control was extremely good. Ninety two per cent of all patients achieved a one year remission by eight years of follow up. Most patients whose seizures were controlled for one year subsequently went on to a second year completely seizure-free. At the end of follow up 82% of patients achieved a two year remission. The duration of follow up was not long enough to allow accurate determination of longer periods of remission but it was apparent that once a remission had occurred the subsequent prognosis was extremely good. There were 76 patients who achieved a two year remission in whom further follow up was available (See page 146) and of these 25 experienced a relapse. In three-quarters of cases these were isolated often related to poor compliance with medication. Most

patients who relapsed subsequently went on to a further prolonged period of remission. Once a two year remission had occurred no patient subsequently developed an intractable seizure disorder.

These findings are almost a complete reversal of the conclusions reached by Rodin (1968) who found that 80% of patients are likely to have a chronic seizure disorder. In contrast it appears that in patients followed prospectively from the onset of the illness as many as four-fifths will experience a prolonged and sometimes permanent remission of seizures. Rodin's other main conclusion was that the percentages of patients who are regarded in terminal remission stand in marked indirect relationship to the length of follow up. In the present study the prognosis improved with increasing duration of follow up (see Figure 3:3) and furthermore the likelihood of relapse decreased the longer seizures were controlled (see Table 3:2).

It is likely in the present study that the treatment methods had a significant impact on seizure control. Patients were started on treatment with either phenytoin or carbamazepine monotherapy and the dosage increased with the help of anticonvulsant level monitoring. If further seizures occurred the dosage was increased until optimal anticonvulsant levels were obtained. Unlike all other prognostic studies a consistant policy of treatment was

used throughout the period of follow up thus ensuring that drugs were used to their maximum effect.

A more important reason for the good results, however, is likely to be patient selection. All previous prognostic studies reported in the literature have been based on the cross sectional selection of cases attending specialised neurology or epilepsy clinics. Such methods of selection will lead to cases of chronic epilepsy being strongly over represented and give rise to an unduly gloomy view of prognosis.

There are a number of important pieces of evidence that support the conclusion that epilepsy is likely to have a good prognosis in a high proportion of cases. Firstly those prognostic studies which have examined epilepsy of short durations have tended to show a better outcome. Kuhl et al (1967) found that in patients with recent onset of seizures (within 5 years from the time of entry into the study) 61% achieved remission. These results approach those found in the present investigation. In the largest prognostic study yet published Okuma & Kumashiro (1981) used a similar method of case selection and found that 58% of patients remitted on treatment.

Probably the strongest evidence to support the conclusions presented here comes from the epidemiology of epilepsy. It

is possible to study the natural history of a disorder by comparing the incidence and prevalence rates. In a disease in which the majority of cases become chronic the sum of the incidence rates over a whole life time (the so called cumulative life time incidence) should equal or approach the point prevalence. As the mortality rates in epilepsy are not high (Hauser, 1975) it is reasonable to use this approach to study the natural history of epilepsy (Zielinsky, 1982; Juul-Jensen & Foldspang 1983). Hauser & Kurland (1975) measured the annual incidence rates for epilepsy in Rochester, Minnesota as 50 per 100,000 of the population. Assuming a 70 year life expectancy this implies that 3.5% of the population could be expected to develop epilepsy at some time during their life. If patients with single seizures were included the figure rose to 5.9%. In a survey of the epilepsies in general practice in England and Wales (Research Committe of the College of General Practitioners, 1960) the cummlative life time incidence for new cases of epilepsy was 4.3%. Results of a similar order of magnitude have also been found in prospective follow up studies of cohorts of live births. In the most extensive of these Ellenberg et al (1984) found that even after exclusion of neonatal seizures 1.3% of children had experienced one or more seizures by the age of 7 years. In comparison the prevalence rates for active epilepsy (usually defined as seizures within the last two years or continuous medication over the same period) are of the

order of 4 to 10 per thousand (Zielinsky, 1982). The ten fold difference between the cumulative incidence and prevalence rates in epilepsy suggest that in only a small proportion of cases does the disease remain active. Studies of epilepsy in the community have been of considerable importance in clarifying our understanding of the prognosis and natural history of epilepsy. Two such studies have been undertaken in adults (Annegers et al, 1979; Goodridge & Shorvon, 1983) and although they were retrospective, the results were in remarkably close agreement to those reported here. Both showed that in patients drawn from an unselected population prolonged and often permanant remissions occurred in as many as three quarters of cases.

3. Prognostic Factors in Newly Diagnosed Epilepsy

Epilepsy is a very heterogeneous illness and it is possible to subdivide the disorder into different groups in which the prognosis may vary widely. The principal division, as proposed by The Commission on Classication and Terminology of the International League against Epilepsy (1981 &1985), is into partial and generalised epilepsies (see Page 21). In clinical practice this is usually made on the basis of seizure type and supported by the results of the electroencephalogram and radiological investigations.

The partial and generalised epilepsies are further subdivided into idiopathic and symptomatic cases in accordance with the presumed aetiology.

There has been no previous attempt to study in detail the importance of these possible subdivisions in predicting the prognosis from the onset of the disorder. In the present study seizure type was one of the most important prognostic indicators. Patients with partial seizures, with or without secondarily generalised attacks, had a significantly poorer outcome. Seventy-three per cent of patients with this seizure type experienced a remission compared to 97% for those with tonic clonic seizures alone (see Table 3:3). Patients with symptomatic epilepsy and associated social and psychiatric handicaps also had a worse prognosis. Although a substantial proportion of patients with any one of these adverse factors still had a good prognosis, a clear picture emerged of the type of patient who responded poorly to medication at the start of the disorder. These were patients in whom there was a high incidence of structural brain disease as shown by a tendency to partial or mixed seizure types, symptomatic epilepsy and associated cognitive and neurological deficits. The initial EEG was of little use in predicting prognosis but those with difusely abnormal background rhythms tended to do poorly, possible because this finding was again associated with cerebral damage. Despite the

overall good prognosis in epilepsy these patients will tend to accumulate in specialised epilepsy clinics with intractable seizure disorders and because of the high prevalence of the disorder they represent a major management problem.

In marked contrast to the controversy that has existed in the literature on the overall prognosis in epilepsy there has been good agreement on the nature of these adverse prognostic factors. Gowers (1881) found, shortly after the introduction of bromides, that patients with minor seizures and those with neurological deficits such as haemiplegia tended to have a worse prognosis. Rodin (1968) concluded that those with temporal lobe seizures had been consistently reported to have a poorer outcome and he also emphasised that the occurrence of multiple seizure types was a particuarly poor prognostic sign. In addition those with a low IQ and an abnormal neurological examination tended to do less well. These adverse prognostic factors are broadly similar to those identified as being of importance in predicting a relapse following a first seizure and a recurrence following anticonvulsant withdrawal (see pages 72 and 107).

4. The Initial Response to Treatment Determines the Long Term Prognosis in Epilepsy

Perhaps one of the most striking observations to arise from this study was the importance of the early response to treatment in determining the long term prognosis of epilepsy. All other studies, being strongly biased towards cases with long standing established seizure disorders, have failed to examine the remission rates at the onset of epilepsy. In the present study three-quarters of all patients who were going to remit were either in or entering a one year remission during the first year of treatment (see Figure 3:3). A further 15% entered remission during the second year of treatment and after this time only occasional cases were subsequently controlled. As was explained above, following a one year remission most went on to a second year seizure free and the subsequent prognosis was extremely good. Thus for the great majority of patients the long term pattern of seizure control was established during the first two years of treatment. Overall 92% of patients achieved a one year remission. In patients who continued to have seizures during the first year of treatment 72% subsequently remitted and of those with seizures in the second year 52% subsequently achieved a one year remission. Thus the longer the seizures continued after the start of treatment the harder they were control (see Figure 3:5). In patients

who failed to achieve a one year remission the outlook was very poor. Ninety per cent had seizures during every two month interval of follow up and most of them went on to develop chronic intractable epilepsy.

If the initial years are of such importance in determining the long term prognosis in epilepsy the question arises as to whether more effective treatment at the onset of the disorder might improve the subsequent outcome and reduce the proportion of those developing chronic epilepy. In the present study patients were treated if they had experienced two or more tonic clonic seizures particularly if these occurred during the space of one year. This is likely to conform to the current practice of most neurologists in this country. In practice, however, many patients had experienced a surprisingly large number of seizures before treatment was given. In Chapter 4 the referral patterns were analysed in a consecutive series of 214 patients with one or more tonic clonic seizures seen over a five year period. Sixty eight per cent of patients presented to medical attention following a first ever seizure which was usually to their general practitioner or a casualty officer within 24 hours of the attack. However, in 43 patients a further seizure occurred during the interval between the first attack and the time of first being seen in the neurology outpatients department. A further delay occurred during which pretreatment

investigations were undertaken. From the data presented in Chapter 3 (see Table 3:3) nearly half of the patients with newly diagnosed epilepsy had experienced four or more tonic clonic seizures before treatment was actually started.

It is possible that such a delay in initiating treatment could lead to a subsequent worsening of prognosis. In patients who experienced four or more pretreatment tonic clonic seizures 83% subsequently remitted (see Table 3:3). In those with two or three seizures the corresponding figures were 96% and 95% respectively. Although this just failed to reach statistical significance it does suggest that prognosis may deteriorate with increasing number of pretreatment seizures.

A number of authors have also reported that prognosis deteriorates with increasing duration of illness and the total number of seizures. Gowers (1881) found that in patients treated with bromides within one year of the onset of the illness 83% had their seizures arrested.These patients are likely to correspond broadly to those with newly diagnosed epilepsy described in Chapter 3. It is striking that his results are almost identical to those reported here using phenytoin and carbamazapine. In those patients with an initial duration of illness lasting 1 to 5 years, 5 to 9 years and greater than 10 years, the

proportion controlled decreased progressively to 73%, 69% and 60% respectively (see Table 3:6). It is of course impossible to be certain that the drugs used prior to bromides were ineffective but there appears to be good agreement in the historical literature that bromides were considerably superior to anything that was previously available (Shorvon, 1987). Gowers' career spanned the introduction of bromides so he was able to observe the outcome in those with a long history of untreated seizures and to subsequently document the dramatic effect that this drug had on the long term prognosis. It is this which made his observations of such particular interest. He subseqently went on to hypothesise that seizures were self propagating, each attack predisposing to the next, a theory he thought to be of importance since he placed it on the first page of his book (Gowers, 1881). A number of modern authors have also found that prognosis deteriorates with increasing number of pretreatment seizures. In the carefully documented Japanese Multi-institutional Study pretreatment seizure number was a highly significant prognostic factor, those with multiple attacks having a worse prognosis. Others have reported similar findings (Maldonando et al, 1987; Johnson, personal communication), and indeed Rodin (1968) included it as one of his major findings following his comprehensive review of the literature (see page 87).

C THE EARLY PATTERNS OF SEIZURE RECURRENCE IN EPILEPSY

There has been no previous attempt in the literature to analyse the patterns of seizure recurrence at the onset of epilepsy or to determine the effects that this may have on the subsequent prognosis. Although a number of authors have examined prognosis in patients presenting following a first seizure the results have been widely conflicting (see Table 1:8) and at variance with the data obtained from the epidemiology of the disorder. This has led to continuing uncertainty about the probability of seizure recurrence, a lack of clear data as to the nature of adverse prognostic factors and widely differing treatment policies.

1. Prognosis following a First Seizure

Estimates of the cumulative incidence of epilepsy suggest that at least 5% of the population will experience one or more afebrile seizure at some time in their life (Hauser & Kurland, 1975). The patient who presents with a single seizure is a common clinical problem yet until recent years there have been relatively few studies that have examined this aspect of prognosis. In the earlier prognostic studies shown in Table 1:8 (Thomas, 1959; Johnson et al, 1972; Saunders & Marshall, 1975; Cleland et al, 1981) the documentation of clinical characteristics

was generally poor and the numbers of patients studied insufficient to allow for accurate determination of prognostic factors. Many have analysed results by measuring crude relapse rates rather than using actuarial probabilities to take account of variable follow up. Treatment policies have differed widely with recent North Americal surveys (Hauser et al, 1982; Camfield et al, 1985; Annegers et al, 1986) reporting that as many as two-thirds patients were given medication following a first seizure.

In Chapter 4 the prognosis following a first ever tonic clonic seizure was assessed in a series of patients referred to a neurology outpatients department. Over a 5 year period 214 patients were consecutively referred with one or more tonic clonic seizures. An initial analysis was undertaken to determine the probability of recurrence, regardless of whether the patients had presented with one or more attacks. After a median follow up of 21 months from the time of the first seizure 64 patients (30%) had experienced only a single seizure and the remaining 150 (70%) had two or more. Patients who developed epilepsy were more likely to have symptomatic seizures and to be under the age of 16 years but otherwise the two groups did not appear to differ in any major respect.

This analysis may have over estimated recurrence rates as it is possible that patients with more than one seizure were more likely to be referred to hospital. In certain instances general practitioners or casualty officers may fail to refer a number of patients who had experienced only a single attack. Studies of how doctors in the community deal with patients who have experienced seizures suggest, however, that this is indeed the case in only a minority of instances (Hopkins & Scrambler, 1977; Goodridge and Shorvon, 1983). The results of epidemiology surveys that have included cases with single seizures are broadly similar to those presented here based on consecutive referrals to a neurology outpatients department. These have all shown that amongst patients identified from an unselected population seizures are likely to be recurrent in 60% to 80% of cases (Table 1:7).

The prognosis of patients who actually present to medical attention with a single seizure will depend crucially upon two factors. Firstly the proportion of those who, following the onset of seizures, actually seek help following the first attack. In the present study 146 patients or 68% of the total were seen by their G.P. or in a casualty department usually within 24 hours of the event. It appears that even with readily available medical facilities about one-third of patients do not seek help until two or more seizures have occurred, possibly because

the first event was not witnessed or occurred during sleep. Others have reported similar findings. In the community based survey of prognosis following a first seizure reported by Annegers et al (1985) 50% of the patients were excluded because they had experienced two or more seizures when first assessed. Clearly if a greater proportion of patients present following the first attack then the observed recurrence rate would be correspondingly higher.

The second factor that can influence the results is the interval of time that elapses between the first seizure and entry into the prognostic study. In the patients described in Chapter 4, 148 were seen within 24 hours of the initial attack. Of these 71% experienced a recurrence by 4 years of follow up. However from this initial 148 patients 43 had already experienced a recurrence by the time of first being seen in the out patients department after a median interval of one month. The remaining 103 patients had a better prognosis with 56% experiencing a further attack by 4 years of follow up (see Figure 4:1).

In many of the prognostic studies shown in Table 1:8 a considerable delay, often of one to two months, occurred before patients were entered into the study. For the reasons explained above these patients are likely to have a signifcantly better prognosis by virtue of the fact that

they have remained seizure free for an appreciable period of time. Todt et al (1985) found that in children seen within two weeks of an initial seizure 59% experienced a recurrence, even after exclusion of any seizures that had occurred after the first year of follow up. Hopkins et al (1988) has recently reported that in patients seen within a week of the first seizure, 52% subsequently developed epilepsy, but in those who remained seizure free after eight weeks the recurrence rate was 22%.

In the present study a number of prognostic factors were analysed by comparing the actuarial percentage of patients experiencing a recurrence. In assessing prognostic factors it is important to emphasise that patients who present with a single seizure are a selected group and differ from those with epilepsy in a number of important respects. Those with partial seizures will be largely excluded as the great majority have had multiple attacks when first seen. Similarly there is likely to be a lower overall incidence of symptomatic seizures and associated handicaps. For this reason the very factors that have been most consistently reported to be of prognostic significance in patients with epilepsy will be largely excluded in series of patients presenting following a single seizure. In the present study those with symptomatic seizures had a worse outcome which is the only factor which has been consistently reported as being of

prognostic importance by those authors who have examined its significance (Hauser et al, 1982; Camfield et al, 1985; Annegers et al, 1986). In clinical practice the time that has elapsed since the initial seizure occurred is likely to be of more use in predicting a subsequent recurrence.

2. Intervals between Untreated Seizures in Patients with Established Epilepsy

In Chapter 5 the intervals between consecutive untreated seizures were analysed in a further 183 cases with two or more tonic clonic seizures. One hundred and one patients experienced two pretreatment seizures, 53 had 3, 18 had 4 and 11 had experienced 5 or more. Amongst all 183 patients the second seizure followed the first in one month in a third of cases, within three months in half the patients and within a year in over four-fifths. In patients in whom the interval between the first and second seizure was less than a month the subsequent prognosis on treatment deteriorated. In addition to being less likely to remain seizure free on treatment the proportion achieving remission was also significantly lower (see Figures 5:1 & 5:2). These findings are in keeping with the observation made in Chapter 3 that pretreatment seizure frequency is an important determinant of the subsequent prognosis on epilepsy.

A striking finding was that in most patients who experienced multiple attacks the median interval between seizures decreased with each seizure that occurred. For all 183 patients the median interval between the first and second seizures was 12 weeks, between the second and third it was 8 weeks, between the third and fourth it had fallen to four weeks and between the fourth and fifth the median interval was 3 weeks. A similar trend was noted when patients with three, four or five seizures were considered separately (see Table 5:3). It was possible to observe consecutive seizure intervals on 122 occasions. In three-fifths of cases the interval decreased, in one fifth it remained the same and in the remaining fifth it increased.

This finding, however, must be considered preliminary and should be interpreted with caution. A significant number of cases, 98 in all, had experienced a large number of seizures that could not be accurately dated and these were excluded from the analysis. In these patients the pretreatment seizure frequency was 0.85 attacks per month compared with 0.5 seizures per month for the 183 patients who were studied. Because of the bias introduced into the initial selection of cases the subsequent seizure intervals might appear to decrease because of regression towards the mean. Furthermore, the timing of initiation of treatment was not made on a randomised basis as it was not

felt ethically justified to withhold treatment in those who had experienced multiple seizures. It is of course possible that if treatment had been withheld the intervals might have lengthened in a significant proportion of cases.

Apart from the data presented here and some observations made by Gowers there appears to be no other study that has analysed this aspect of the early prognosis of epilepsy. The initial results suggest that the early patterns of seizure recurrence are of considerable importance in determining the subsequent prognosis in epilepsy. Goodridge & Shorvon (1983) have reported in cases identified from the community that epilepsy is usually a short lived disorder with most patients experiecing about ten seizures in total. The findings presented here suggest that the interval between the first and second seizure might be an important determinant of the length of time during which the illness is likely to remain active. Further studies are needed both in treated and untreated patients to examine the early patterns of seizure recurrence in patients with newly diagnosed epilepsy and to clarify the possible effects on subsequent prognosis.

3 The Natural History of Untreated Epilepsy

It was shown in the previous sections that following the initiation of anticonvulsant medication the majority of patients with epilepsy rapidly enter a prolonged period of seizure control, usually within one to two years of starting treatment. The subsequent outlook is extremely good and in a significant proportion of cases the remission of seizures may indeed be permanent. In contrast, in those who continue to have seizures, the prognosis deteriorates the longer the disorder remains active. It remains uncertain, however, to what extent these findings represent the natural history of the disorder and what proportion of cases might, without treatment, have remitted spontaneously.

The clearest statement on the prognosis of untreated epilepsy was written by Gowers over a century ago. In describing the course and prognosis of epilepsy he paid particular attention to the onset of the disorder. He stated clearly that following a first seizure the majority of patients will develop epilepsy. He went on to give an analysis of the intervals between the first and second seizures in a 160 cases and concluded that the second seizure followed the first within a month in one third of patients, within a year in another third and exceeded one year in the remaining third (see Table 1:6). Furthermore,

when the disease was confirmed and multiple attacks had occurred the interval from freedom from seizures did not exceed one month in 80% of cases. This observation was based on clinical data from 688 patients, the majority untreated. Gowers went on to say, in a widely quoted statement that spontaneous remission of epilepsy was "an event too rare to be reaonably anticipated in any given case".

There are always difficulties in interpreting information in the historical literature. It is uncertain as to the precise group of patients Gowers was referring to when he made this statement. The literature is full of erroneous conclusions concerning the prognosis of epilepsy based on selected or unrepresentative groups of patients. It is unlikely, however, that he was referring exclusively to those with chronic intractable epilepsy. It had been known for centuries that these patients would not remit, either with or without treatment. Gowers practice was evidently enormous and his diligence and clarity of clinical desription unequalled. He studied the early prognosis of epilepsy in considerable detail and his conclusions, or at least those which have been possible to test, have proved largely correct. His observation that the introduction of bromides had a dramatic effect on prognosis suggest that in discussing the natural history of epilepsy he was not confining himself to patients with intractable seizures.

With the current provision of medical services the great majority of patients who develop epilepsy receive effective treatment early in the course of the disorder. Our ability to study the natural history of untreated epilepsy is severly limited. Zielinsky (1976) has reported in a field study carried out in Warsaw that as many one third of patients who developed seizures did not appear to receive any treatment. Similar results were found in a field survey in Iceland (Gumundsson, 1966). The patients identified by Zielinsky were largely unknown to the established medical facilities and the prognosis was not commented upon. It is likely furthermore that patients who do not seek help from doctors will be a selected sample, perhaps containing a high proportion of cases with acute symptomatic seizures such as those occurring in the context of alcohol withdrawal. Similarly epidemiology surveys carried out amongst primitive populations where modern drugs are not freely available have not commented upon prognosis (Mathai et al, 1968).

Shorvon et al (1985) have argued that because of these uncertainties there is reasonable grounds for conducting a placebo controlled trial of anticonvulsants in newly diagnosed epileptic patients comparing the outcome in those treated and untreated. The possibility of conducting such a trial will be considered in a later section but suffice it to say there appears to be

insurmountable ethical objections to withholding a treatment of known efficacy from patients with established epilepsy.

The data on the early patterns of seizure recurrence reported here suggest that at the onset of epilepsy spontaneous remission is likely to be an unusual event. Despite the controversy which has existed in the literature it does indeed appear that following a first seizure the majority of patients will experience a recurrence. It seems most unlikely, therefore, that a significant proportion of those patients with two, three or more seizures would remain seizure free without treatment. Indeed in patients with established epilepsy (defined here as two or more attacks occurring within the space of one year) nearly four-fifths experience at least one more seizure, even with effective treatment (see figure 3:1). The decreasing interval between successive untreated seizures and the high seizure frequency in patients with multiple attacks also suggest that spontaneous remission is unlikely.

It is possible that in some patients the natural history may be a burst of seizures, perhaps four or five attacks occurring within the space of a year, followed by spontaneous and permanent remission. This could not be excluded on the basis of the current knowledge of the

early prognosis of epilepsy. Presumably such cases could only be identified with certainty by witholding treatment in a series of patients with newly diagnosed epilepsy. There are a number of patients where isolated seizures appear to occur, sometimes separated by a period of many years. These probably account for no more than about one tenth of cases of epilepsy (see Table 5:2). In the author's experience patients in whom multiple seizures occur in rapid sucession followed by a period of prologed remission are exceptionally rare in clinical practice. It must be admitted that the arguments considered above are all of an indirect nature, but on the basis of an analysis of the patterns of seizure recurrence at the onset of epilepsy, there is little evidence to suggest that many patients would remit spontaneously.

D. IMPLICATIONS FOR THE TREATMENT OF EPILEPSY

A number of important conclusions concerning the treatment of epilepsy arise from the observations on the early prognosis of epilepsy considered above. As was shown in Chapter 1 many unsatisfactory and irrational aspects of the drug treatment of epilepsy remain. There is remarkably little reliable information to be found in the literature on the relative efficacy and toxicity of the major established anticonvulsant drugs (Coatsworth, 1971; Gram et al, 1982; Shorvon et al 1981; Chadwick and Turnbull, 1985). In patients who fail on the initial drug there has been no prospective evaluation of the proportion of patients who subsequently respond to additions or changes in medication. The widespread use of polytherapy continues to be a feature of the treatment of epilepsy despite the fact that there is little evidence of its value (Reynolds & Shorvon, 1981). The disadvantages in terms of drug interactions, chronic toxicity and deteriorating seizure control, however, have been manifestly proven.

Once treatment is initiated continuous medication is given over a number of years and those with intractable seizure disorders may receive lifelong treatment with large number of drugs often given in combination. The timing of the initiation of treatment has never been the subject of

prospective evaluation although it is apparent that the early prognosis of epilepsy is of considerable importance in determining the subsequent outcome. A rational basis for the early treatment of epilepsy must be based on an understanding of the early patterns of seizure recurrence yet this aspect of the natural history of epilepsy has received scant attention in the literature.

1. The Design and Analysis of Anticonvulsant Trials

The most important reason for the lack of clear data on the comparative efficacy and toxicity of the established drugs has been the deficiencies in design of anti-convulsant trials. In his review of the literature Coatsworth (1971) concluded that sufficient studies were not to be found to confidently test the relationship between the use of a drug and its influence on a particular seizure type. Gram et al (1982) reached a similar conclusion and identified a number of deficiencies in design which included marked heterogenecity of patient groups, "add on" designs with concurrent treatments being changed during the course of a trial and cross over studies which failed to include a wash out period. Shorvon et al (1981) have emphasised the difficulties in making appropriate comparisons between drugs on the basis of reduction in seizure frequencies measured over short periods of time.

The most striking deficiency, however, has been that anticonvulsant trials are usually undertaken in patients with chronic intractable seizure disorders. It must surely be unlikely that meaningful results concerning the efficacy of a particular treatment will be established if trials are conducted in a group of patients who are essentially drug resistant. Esquirol's experience at the Salpetriere over a hundred years ago is still relevant (Temkin, 1971). Twice a year thirty patients were subjected to some new form of treatment. Although seizure control improved for one or two months after this period they invariably returned and a cure was never obtained (see page 80). This is a common experience to anyone who has conducted anticonvulsant trials in drug resistant patients. Rodin (1982) has emphasised that even after admission to hospital and a period of intensive assessment using all the modern facilities available, the great majority of patients failed to achieve a lasting improvement in seizure control.

Some of these difficulties may be overcome by carrying out anticonvulsant trials in newly diagnosed patients with previously untreated epilepsy. The drugs are given as monotherapy avoiding unpredictable drug interactions and the need to employ cross-over designs and wash out periods. Similarly it is only in this manner that a clear understanding of the comparative toxicity of individual

compounds will be established. As was shown in Chapter 3 the early years of treatment are of considerable importance in determining the outcome in epilepsy as the great majority of remissions occur during the first one to two years. It is only by comparing the drugs during this crucial period of the natural history of the disorder that meaningful data on the comparative efficacy will be likely to be established.

A number of trials have now been undertaken, or are currently in progress, and important indications are beginning to emerge. Turnbull et al (1982) found that sodium valporate and phenytoin were equally effective in controlling tonic clonic seizures. Mattson et al (1985) in a larger trial comparing phenobarbitone, primidone, phenytoin and carbamazapine in patients with previously untreated epilepsy. Although clear conclusions concerning control of partial seizures were not available in the first of these trials there were twice as many treatment failures in patients with this seizure type who received sodium valproate. In the latter study, treatment outcome appears to have been more closely related to the occurrence of acute toxicity as all patients had anticonvulsant levels within the optimum range and dosages were increased until toxicity occurred. Despite this difficulty it was found that treatment with carbamazapine was more likely to lead to complete control of partial

seizures than barbiturates, with phenytoin being of intermediate efficacy.

The undertaking of these trials call for a considerable investment of time and effort as patients must be recruited over a number of years and prolonged and prospective follow up is needed. Analysis of outcome in terms of complete seizure control from the start of treatment is probably not ideal as although the majority of patients experience at least one further seizure after starting treatment the majority subsequently achieve a prolonged period of remission. The outcome in those who fail on the initial drug has not been analysed in detail. Mattson et al (1985) reported that only 11% responded to a second added drug and that improvements in seizure control usually occurred at the cost of increased toxicity. This trial also included the use of primidone which is not widely used to treat epilepsy at least in this country.

The initial indications that there may be significant differences between the drugs in controlling partial seizures are of considerable importance. It is this group who are more prone to develop chronic intractable epilepsy. If these results are confirmed in more extensive studies, involving both children and adults, they will have considerable implications for the treatment of epilepsy. If there is indeed no difference between the

major established drugs in controlling tonic clonic seizures then the choice of drug will have to be made on the basis of other factors such as price, dosaging and pharmacokinetic properties and in particular drug toxicity. Amongst the latter, effects on cognitive functions may be of particular importance as there are already indications that there are signficant differences between the drugs (Reynolds et al, 1983).

2. A Randomised Study of the Effects of Early and Delayed Treatment in Newly Diagnosed Epilepsy

Perhaps the single most important question to arise from a study of the early prognosis of epilepsy is whether earlier or more effective treatment at the onset of the disorder might improve the prognosis and enhance the probability of obtaining a cure. The theoretical basis for such a hypothesis has already been considered in the previous sections.

Although there is considerable heterogenecity of outcome in epilepsy there is good evidence that in the majority of cases spontaneous remission of the disorder is an unusual event. Following a first seizure between 60% and 80% of patients are likely to experience a recurrence and if left untreated the intervals between consecutive attacks appear

to decrease with each seizure that occurs. If the tendency of the disorder at the onset is to undergo spontaneous remission then a high proportion of cases would remain completely seizure free after starting treatment. This, however, does not appear to be the case as at least 80% of patients are likely to experience at least one more attack. In comparison once treatment has been started over 80% rapidly enter a period of prolonged remission. There is evidence from epidemiological and community based surveys that in a substantial proportion of cases remission of seizures may indeed be permanent. The implication of these two observations must be that anticonvulsants not only suppress seizures but in doing so they may actually alter the natural history of epilepsy and bring about a cure.

Shorvon (1984) has pointed out that Gowers was aware of this implication when he observed that spontaneous remission was very unusual and that the introduction of bromides had a very major impact on the prognosis of epilepsy. Indeed it is probably on this basis that he went on to propose that seizures were self propagating each attacks predisposing to the next.

It is the current practice of most neurologists, at least in this country, to await the occurrence of two or more seizures before starting treatment. There is a strong

intuitive appeal for this position as epilepsy is, by definition, the occurrence of two or more seizures and it would appear reasonable to withhold treatment until the disease is established. This practice, however, has never been universal, nor does it appear to be founded upon any reasoned discussion anywhere in the literature. Herpin's conclusions on the efficacy of zinc oxide were subjected to scathing criticism by Delasuive on the basis that he treated patients following a first seizure (Temkin, 1971). A number of recent prognostic studies of patients presenting with a single seizure have reported that as many as two-thirds were treated (see Table 1:10). Reynolds (1984) has observed that this practice may be based more upon medico-legal considerations rather than a sound understanding of the early prognosis of epilepsy. Current neurological practice in this country may be a reflection of the fact that the majority of patients are seen months after the first seizure when the majority of patients will have already developed epilepsy.

In this respect it is of interest to analyse the referral and treatment practices in patients with one or more seizures referred to a district general hospital neurological department. Out of a total of 214 patients with tonic clonic seizures seen over a four year period described in Chapter 3, 146 or 68% of the total had presented to medical attention following a first attack.

This may well have been an underestimate as the analysis was by nature retrospective. The occurrence of a first ever tonic clonic seizure is likely to be a dramatic event and the majority of patients would be expected to seek help early. Indeed half of them were seen within hours in the casualty department and the remaining contacted their general practitioner within 24 hours. In comparison once the disorder was established there appeared to be a certain lack of urgency in initiating treatment. Only 13 were treated following the first attack. Amongst the 256 patients with tonic clonic seizures considered in Chapter 4, 69 had 3 pre-treatment seizures, 33 had 4, and 46 suffered 5 or more, often occurring over a considerable period of time (see Table 5:1). These data were gathered during a time when the department was actively engaged with the rapid identification and investigation of newly diagnosed epileptic patients for inclusion into randomised trials of anticonvulsant medication.

The hypothesis that early treatment could favourably affect the prognosis of epilepsy could only be tested with certainty by mounting some form of trial which involved a group randomised to early intervention. There are a number of different designs.

The possibility of carrying out a placebo controlled trial in newly diagnosed epilepsy has been the subject of debate

(Shorvon et al, 1985). There is, however, insummountable ethical objection to such a study. The hypothesis under question is not whether anticonvulsants work, for there is ample evidence from a variety of sources that they do, but whether early treatment improves the long term prognosis. The only basis on which such a trial could be mounted would be that a significant proportion of cases might remit spontaneously and that the disadvantages of treatment particuarly in terms of anticonvulsant toxicity outweigh the possible advantages. Although it is feasible to argue that such considerations might apply in certain childhood epilepsies such as rolandic epilepsy or petit mal, there is little evidence to support this position in the majority of cases arising in either adults or children. Furthermore the great majority of patients with newly dignosed epilepsy experience only minimal anti-convulsant toxicity if the drugs are given as monotherapy with the increases in dosage made with the help of anticonvulsant level monitoring (Elwes & Reynolds 1988).

It is only feasible to mount a trial where current medical practices are open to question on theoretical or practical grounds. This does appear to be the case with the current practice of those with responsibility in primary care withholding treatment in cases of recent onset of seizures and referring patients to hospital for investigation.

Hopkins et al (1988) have recently observed that these investigations are of limited use in either establishing the aetiology or predicting the subsequent prognosis. The recurrence rate with patients with one attack seen within days is of the order of 60%-80%. Ironically, the conclusion that a single seizure was likely to be an isolated event of little clinical significance arose from experience based on these very same practices with specialists seeing the patients months after the initial event.

Such a study would have to be community based, or carried out in close association with casualty officers or general practitioners, with the decision to give or withhold treatment made on a randomised basis. Although such a study would provide information as to whether treatment reduces the probability of recurrence following a first attack (a question which has never been the subject of a randomised trial) it need not necessarily be confined to patients with single seizures.

The practical difficulties in design and analysis and the possible consequences of such a trial require careful consideration. There are certain circumstances in which it is more appropriate on clinical grounds to withhold treatment. In a high proportion of cases referred to hospital with episodes of loss of consciousness the

diagnosis is syncope rather than epilepsy. In those with undoubted seizures there may be a clear history of significant precipitating factors such as lack of sleep, alcohol or drug abuse. Treatment may also be withheld on the grounds that the patient would be considered likely to comply poorly with medication. It would have to be accepted that if treatment were begun by those with less experience in assessing possible cases of epilepsy, then the decision to treat would be wrong in a higher proportion of cases. The tendency to propagate the unsatisfactory practice of trials of medication would have to be resisted. This difficulty may not be insurmountable as in those cases in which there is little doubt as to the diagnosis the majority are likely to have been correctly assessed prior to hospital referral. Furthermore, such a trial would be likely to enhance diagnostic accuracy.

Another consideration is that treating single seizures would de facto imply a diagnosis of epilepsy leading to unnecessary adverse consequences. This need not be the case, however, as the definition of epilepsy for the purposes of driving and insurance would not be under question. Indeed, if early treatment was effective in reducing a seizure recurrence, a number of patients would escape the diagnosis altogether. A similar consideration applies to possible difficulties with employment as the assumed handicap relates to the occurrence of seizures

themselves particularly if they lead to injuries or occur at work.

A more difficult objection to the study would be the selection bias of patients entered and the possible impact of poor compliance with medication. The patients identified for early treatment would, more likely, be those who had experienced tonic clonic seizures. The majority of these patients suffer from idiopathic epilepsy and remission rates are likely to be extremely high, even with the current practice of withholding treatment until multiple attacks have occurred. Although early treatment might shorten the duration of what, in a high proportion of cases, may be a curable disorder, it would not test the hypothesis as to whether early treatment stops the development of chronic intractable epilepsy. Furthermore because of the highly variable outcome in epilepsy careful consideration would need to be given to the methods of analysing such a trial.

There is evidence from the data presented in Chapter 5 and other analyses (Shope, 1981; Liske & Green, 1985) that poor compliance with medication is an important cause of treatment failure in epilepsy. This consideration has proved to be a major obstacle in establishing the use of prophylactic medication following head injuries (Blackwood & McQueen, 1983). Although not strictly comparable, a

study involving treatment following a single seizure might encounter similar problems.

Despite these possible difficulties, a randomised study of the effects of early and delayed treatment on prognosis is likely not only to be feasible but of much theoretical interest and practical importance. If Gowers' hypothesis proves to be correct it would be an important advance in our understanding of epilepsy and would have considerable implications for the treatment of one of the commonest neurological disorders.

REFERENCES

Aidie WJ.
Pyknolepsy: a form of epilepsy occurring in children with a good prognosis.
Brain 1924; 47:96-102

Albright P, Bruni J.
Reduction of polypharmacy in epileptic patients.
Arch Neurol 1985; 42:797-9.

Alstrom CH.
A study of epilepsy in its clinical, social and genetic aspects.
Acta Psychiat Neurol Scand 1950; suppl 63:1-284.

Andrewes DG, Bullen JG, Thomlinson L, Elwes RDC, Reynolds EH. A comaritive study of the cognitive effects of phenytoin and carbamazepine in new referrals with epilepsy. Epilepsia 1986;27:128-34.

Annegers JF, Hauser WA, Elveback LR.
Remission of seizures and relapse in patients with epilepsy.
Epilepsia 1979; 20:729-37.

Annegers JF, Shirts SB, Hauser WA, Kurland LT.
Risk of recurrence after an initial unprovoked seizure. Epilepsia 1986; 27:43-50.

Annegers JF, Hauser WA, Shirts SB, Kurland LT.
Factors prognostic of unprovoked seizures after febrile convulsions. N Engl J Med 1987; 316:493-8.

Arieff AJ.
Twelve year resume in a clinic for epilepsy.
Dis Nerv System 1951; 12:19-22.

Beaumanoir A (a).
The Landau-Kleffner Syndrome. In: Roger J, Dravet C, Bureau M, Dreifuss FE, Wolf P, eds. Epileptc syndromes in infancy, childhood and adolescence.
London: John Libby, 1985:181-91.

Beaumanoir A (b).
The Lennox-Gastaut syndrome. In: Roger J, Dravet C Bureau M, Dreifuss FE, Wolf P, eds. Epileptic syndromes in infancy, childhood and adolescence. London: John Libby, 1985:89-99.

Bellman M.
Infantile spasms. In: Pedley TA, Meldrum BS, eds. Recent advances in epilepsy, number one. Edinburgh Churchill Livingstone, 1983:113-38.

Berkovic SF, Andermann F.
The progressive myoclonus epilepsies. In; Pedley TA, Meldrum BS, eds. Recent advances in epilepsy, number three. Edinburgh: Churchill Livingstone, 1986: 157-187.

Blackwood DHR, McQueen JK.
Anticonvulsant prophylaxis after head injiry. In: Shorvon SD, Birdwood GFB, eds. Rational approaches to anticonvulsant drug therapy. Berne: Hans Huber, 1984:65-73.

Blom S, Heijbel J, Bergfors PG.
Benign epilepsy of children with centro-temporal EEG foci: prevalence and follow-up study of 40 patients. Epilepsia 1972; 13:609-19.

Blom S, Heijbel J, Bergfors PG.
Incidence of epilepsy in children: a follow-up study three years after a first seizure. Epilepsia 1978; 19:343-50.

Blom S, Heijbel J.
Benign epilepsy of children with centrotemporal EEG foci: a follow-up study in adulthood of patients initially studied as children. Epilepsia. 1982; 23:629-32.

Blume WT, David RB, Gomez MR.
Generalised sharp and slow wave complexes: assosciated clinical features and long term follow up. Brain 1973; 96:289-306.

Bouma PAD, Peters ACB, Arts RJHM, Stijnen Th, Van Rossum J.
Discontinuation of antiepileptic therapy: a prospective study in children. J Neurol Neurosurg Psychiatry 1987; 50:1579-83.

Bourgeois BFD, Prensky AL, Palkes HS, Talent BK, Busch SG.
Intelligence in epilepsy: a prospective study in children. Ann Neurol 1983; 14:438-44.

Bridge EM.
Epilepsy and convulsive disorders in children. New York: McGraw Hill, New York, 1949.

Brock JT, Dyken M.
The anticonvulsant activity of chlordiazepoxide and Ro 5-2807. Neurology (NY) 1963; 13:59-65

Brorson LO, Wranne L.
Long-term prognosis in childhood epilepsy: survival and seizure prognosis.
Epilepsia 1987; 28:324-30.

Callaghan N, O'Callaghan M, Duggan B, Feely M.
Carbamazepine as a single drug in the treatment of epilesy. J Neurol Neurosurg Psychiatry 1978; 41: 907-12.

Callaghan N, Kenny RA, O'Neill B, Crowley M, Goggin TA. A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated epilepsy.
J Neurol Neurosurg Psychiatry 1985; 48:639-44.

Camfield PR, Camfield CS, Dooley JM, Tibbles JAR, Fung T, Garner B.
Eipilepsy after a first unprovoked seizure in childhood. Neurology 1985; 35:1657-60.

Carraz G, Gau R, Chateau R, Bonin J.
Communication a propos des premiers essais clinics sur l'activite anti-epileptique de l'acide n-dipropylacetique (sel de Na+).
J Ann Med Psychol (Paris) 1964; 122:577-84.

Cavazutti GB.
Epidemiology of different types of epilepsy in school age children of Modena, Italy. Epilepsia 1980; 21:57-62.

Cavazzuti GB, Capella L, Nalin A.
Longitudinal study of epileptiform EEG patterns in normal children.
Epilepsia. 1980; 21:43-55.

Caveness WF, Meirowsky AM, Rish BL et al.
The nature of post-traumatic epilepsy.
J Neurosurg 1979; 50:545-53.

Cavazutti GB, Ferrari P, Lalla M.
Follow-up study of 482 cases with convulsive disorders in the first yesr of life.
Develop Med Child Neurol 1984; 26:425-37.

Chadwick D.
The discontinuation of antiepileptic therapy.
In: Pedley TA, Meldrum BS, eds. Recent advances in epilepsy, number 2. Edinburgh: Churchill Livingstone, 1985:111-24.

Chadwick DW.
Overuse of monitoring of blood concentrations of antiepileptic drugs. Br Med J 1987; 294:723-4.

Chadwick D, Hallett M, Jenner P, Marsden CD.
Treatment of posthypoxic action myoclonus: Implications for the pathophysiology of the disorder. In: Fahn S, Marsden CD, van Woert MH, eds. Advances in Neurology 1984; 34:183-90.

Chadwick D, Reynolds EH.
When do epileptic patients need treatment? Starting and stopping medication Br Med J 1985; 290:1885-8

Chadwick D, Turnbull DM.
The comparitive efficacy of antiepileptic drugs for partial and tonic clonic seizures.
J Neurol Neurosurgery Psychiatry 1985; 48:1073-7.

Chesterman P, Elwes RDC, Reynolds EH.
Failure of monotherapy in newly diagnosed epilepsy
In: Wolf P, Dam M, Janz D, Dreifuss FE, eds. Advances in epileptology, Vol16. New York: Raven Press, 1987:461-4.

Cleland PG, Mosquera I, Steward WP, Foster JB.
Prognosis of isolated seizures in adult life.
Br Med J. 1981; 283:1364.

Coatsworth JJ.
Studies on the clinical efficacy of marketed antiepileptic drugs. NINDS monograph No 12. Washington: U.S. Government Printing Office, 1971

Commision on Classificaton and Terminology of the International League Against Epilepsy.
Proposal for revised clinical and electroencephalo -graphic classification of epileptic seizures.
Epilepsia 1981; 22:489-501.

Commision on Classificaton and Terminology of the International League Against Epilepsy.
Proposal for classification of epilepsies and epileptic syndromes. Epilepsia 1985; 26:268-78

Costeff H.
Convulsions in childhood. Their natural history and indications for treatment. N Eng J Med 1965; 273:1410-3.

Currie S, Heathfield KWG, Henson RA, Scott DF.
Clinical course and prognosis of temporal lobe epilepsy. A survey of 666 patients.
Brain. 1971; 94:173-90

Currier RD, Kooi KA, Saidman LJ.
Prognosis of"pure"petit mal. A follow-up study.
Neurology 1963; 13:959-67.

Dalby MA.
Epilepsy and 3 per second spike and wave rythms. A clinical, electroencephalographic and prognostic analysis of 346 patients. Acta Neurol Scand 1969; 45(suppl 40).

Dalby MA.
Behavioral effects of carbamazepine. In:Penry JK, Daly DD, eds. Avances in neurology, vol 11. Complex partial seizures and their treatment.
New York: Raven Press, 1975:331-44.

Dalla Bernardina B, Chiamenti C, Capovilla G et al
Benign partial epilepsy with affective symptoms.
In: Roger J, Dravet C, Bureau, Dreifuss FE, Wolf P
Epileptic syndromes of infancy, childhood and adolescence. London: John Libby, 1985:171-5

Dam M.
Phenytoin toxicity. In: Woodbury DM, Penry JK, Pippenger CE, eds. Antiepileptic drugs. New York: Raven Press, 1982:247-56.

Davis CE.
The effect of regression to the mean in epidemiologic and clinical studies. Am J Epidemiol 1976; 104:493-8.

Dodrill CB, Troupin AS.
Psychotropic effects of carbamazepine in epilepsy. A double-blind comparison with phenytoin. Neurology 1977; 27:1023-28.

Dreifuss FE.
Sodium Valproate: a reappraisal. In Pedley TA, Meldrum BS, eds. Recent advances in epilepsy, number one. Edinburgh: Churchill Livingstone, 1983: 35-46.

Eeg-Olofsson O, Petersen I, Sellden V.
The development of the EEG in normal children from age of 1 through 15 years. Paroxysmal activity. Neuropaediatrie 1971; 2:375-404.

Ellenberg JH, Hirtz DG, Nelson KB.
Age at onset of seizures in young children. Ann Neurol 1984; 15:127-34.

Elwes RDC, Johnson AL, Shorvon SD, Reynolds EH.
The early prognosis of epilepsy.
In: Parsonage M, Grant RHE, Craig AG, Ward AA, eds Advances in epileptology. New York: Raven Press, 1982:133-41.

Elwes RDC, Shorvon SD, Reynolds EH.
Epileptics refractory to anticonvulsants.
Neurology 1984; 34:263.

Elwes RDC, Johnson AL, Shorvon SD, Reynolds EH.
The prognosis for seizure control in newly diagnosed epilepsy.
N Engl J Med 1984; 311:944-7.

Elwes RDC, Chesterman P, Reynolds EH.
Prognosis after a first untreated tonic-clonic seizure. Lancet 1985; ii:752-3.

Elwes RDC, Reynolds EH.
Should people be treated after a first seizure?
Arch Neurol 1988; In press.

Emerson R, D'Souza BJ, Vinning EP, Holden KR, Mellits ED, Freeman JM.
Stopping medication in children with epilepsy. Predictors of outcome. N Eng J Med 1981; 304: 1125-9.

Feely MP, O'Callaghan M, O'Driscoll D, Callaghan N
Sulthiame in previously untreated epilepsy.
Ir J Med Sci 1982; 151:175-9.

Feely M, Duggan B, O'Callaghan M, Callaghan N.
The therapeutic range for phenytoin-a reappraisal.
Ir J Med Sci 1982; 148:44-9.

Forster C, Schmidberger G
Prognose der epilepsie im kindersalter nach absetz en der medikation.
Manatsschr Kinderheilfd 1982; 130:225-8.

Friedlander WJ.
Putnam, Merritt and the discovery of dilantin.
Epilepsia 1986; 27(suppl 3):1-21.

Fromm GH, Crumrine P.
Ethosuxumide: an update. In: Pedley TA, Meldrum BS eds. Recent Advances in Epilepsy, Number Three. Edinburgh: Churchill Livingstone, 1986: 279-94

Gastaut H.
The Lennox-Gastaua syndrome. Comment on the syndr-ome's terminology and nosological position amoungst the secondary generalised epilepsies.
EEG Clin Neurophysiol 1982; suppl 35:71-84.

Gastaut H.
Benign partial epilepsy with with occipital par-oxysms. In: Roger J, Dravet C, Bureau M, Dreifuss FE, Wolf P,eds.Epileptic syndromes in infancy, childhood and adolescence. London: Libby, 1985.

Gastaut H, Dravet C, Loubier D et al.
Evolution clinique et pronostic du syndrome de Lennox-Gastaut. In: Lugaresi E, Pazzaglia P, Tassinari CA, eds. Evolution and prognosis of epilepses. Bologna: Aulo Gaggi, 1973:133-54.

Gastaut H, Gastaut JL, Silva GE, Sanchez GRF.
Relative frequency of different types of epilepsy: a study employing the classification of the international league against epilepsy.
epilepsia 1975; 16:457-61.

Gastaut H, Zifkin BJ, Mariani E, Puig JS.
The long-term course of primary generalised epilepsy wit persisting absences.
Neurology 1986; 36:1021-28.

Gibberd FB, Dunne JF, Handley AJ, Hazelman BL.
Supervision of epileptic patients taking phenytoin
Br Med J 1970; i:147-9.

Gibbs FA.
New drugs of value in the treatment of epilepsy.
Ann Intern Med 1947; 27:548-54.

Gibbs FA, Gibbs EL.
Atlas of electroencephalography, vol 2, Epilepsy.
Addison-Wesley: Cambridge, Mass. 1952.

Gibbs EL, Gibbs FA.
Good prognosis of mid-temporal epilepsy. Epilepsia 1959-1960; 1:448-53.

Gibbs FA, Gibbs EL, Lennox WG.
Epilepsy: a paroxysmal crebral dysrhythmia.
Brain 1937; 60:377-88.

Gidderd FB
The prognosis of petit mal.
Brain 1966; 89:531-8.

Glaser GH.
Diphenylhydantoin: Toxicity. In Woodbury DM, Penry JK, Schmidt RP, eds. Antiepileptic drugs. New York Raven Press, 1972:219-26

Goodridge DMG, Shorvon SD.
Epileptic seizures in a population of 6000.
II: Treatment and prognosis.
Br Med J 1983; 287:645-7.

Gordon N.
The natural history of petit mal epilepsy.
Develop Med Child Neurol 1965; 7:537-42.

Gowers WR.
Epilepsy and other chronic convulsive disorders.
London: Churchill, 1881.

Gram L, Drachmann Bentsen K, Parnas J, Flachs H.
Controlled trials in epilepsy: a review.
Epilepsia 1982; 491-521.

Groh Ch.
Zur frage der heilbarkeit kindlicher epilepsie.
Klin Wochenschr 1975; 87(suppl 40):1-23

Gross W.
Uber den ausgang der genuinen epilepsie (auf grund katamnestischer erhebungen).
Archiv Psychiat Nerv 1930; 90:765-76.

Guelen PJM, Van Der Kleijn E, Woudstra U.
Statistical analysis of pharmacokinetic parameters in chronic epilepsy. In Schnieder H et al, eds.
Clinical pharmacology of antiepileptic drugs.
Springer-Verlag: Berlin, 1975:2-10.

Gumundson G.
Epilepsy in Iceland.
Acta Neurol Scand 1966; 43(suppl 25).

Haabermas S.
Uber die prognose der epilepsie.
Allg. ZF Psychiat 1901; 58:243-53.

Hachinski V.
Management of a first seizure.
Arch Neurol 1986; 43:1290.

Hart RG, Easton D.
Seizure recurrence after a first, unprovoked seizure. Arch Neurol 1986; 43:1289-90.

Hauptmann A.
Luminal bei epilepsie.
Munch Med Wochenschr 1912; 59:1907-9.

Hauser WA.
Should people be treated following a first seizure? Arch Neurol 1986; 43:1287-8.

Hauser WA, Kurland LT.
The epidemiology of epilepsy in Rochester, Minnessota, 1935 through 1967. Epilepsia 1979; 16:1-66

Hauser WA, Anderson VE, Loewenson RB, McRoberts SM
Seizure recurrence after a first unprovoked seizure.
N Engl J Med. 1982; 307:522-8.

Hauser WA, Annegers JF, Elveback LR.
Mortality in patients with epilepsy.
Epilepsia 1980; 21:399-412.

Heijbel J, Blom S, Bergfors PG.
Benign epilepsy of children with centrotemporal EEG foci: a study of incidence rate in outpatient care. Epilepsia 1975; 16:657-64.

Heller A, Chesterman P, Elwes RDC et al.
A comparitive monotherapy trial in aduld epilepsy.
Presented at the 17th Epilepsy International
Congress, Jerusalem, 1987.

Hertoft P.
The clinical, electroencepalographic and social
prognosis of petit mal epilepsy.
Epilepsia 1963; 4:298-314.

Hirtz DG, Ellenberg JH, Nelson KB.
The risk of recurrence of nonfebrile seizures in
children. Neurology (Cleveland) 1984; 34:637-41.

Hollowach J, Thurston DL, O'Leary JL.
Petit mal epilepsy.
Pediatrics 1962; 30:893-901.

Hopkins A.
The first seizure, and the diagnosis of epilepsy.
In: Hopkins A, ed. Epilepsy. London: Chapman and
Hall, 1987:151-68.

Hopkins A, Scrambler G.
How doctors deal with epilepsy.
Lancet 1977; i:183-6.

Hopkins A, Garman A, Clarke C.
The first seizure in adult life. The value of
clinical features, electroencephalography and
computerised tomographic scanning in prediction of
seizure recurrence. Lancet, 1988; i:721-6.

Hughlings Jackson J (1873).
On the anatomical, physiological and pathological
investigations of epilepsies. In: Taylor J, ed.
Selected writings of John Hughlings Jackson, Vol
one. London: Hodder and Stroughton 1931:90-117.

Hughlings Jackson J, Colman WS.
Case of epilepsy with tasting movements and
"dreamy states"-very small patch of softening in
the left uncinate gyrus. Brain 1898 21:580-90.

James KE.
Regression towards the mean in uncontrolled studies. Biometrics 1973; 29:121-30.

Janz D.
Results of long term treatment in epilepsy.
Riv Pat Nerv Ment 1972; 93:188-201.

Janz D, Sommer-Burkhardt EM.
Discontinuation of antiepileptic drugs in patients with epilepsy who have been seizure-free for more than two years. In: Janz D ed. Epileptology.
Stuttgart: Thieme, 1976:228-34.

Jeavons PM, Bower DB, Dimitrakoudi M.
Long-term prognosis of 150 cases of "West Syndrome". Epilepsia 1973; 14:153-64.

Jeavons PM.
West syndrome: Infantile spasms. In: Roger J, Dravet C, Bureau, Dreifuss FE, Wolf P, eds.
Epileptic syndromes in infancy, childhood and adolescence. London: John Libby, 1985:42-50.

Johnson LC, De Bolt WL, Long MT et al.
Diagnostic factors in adult males following initial seizures. Arch Neurol 1972; 27:193-7.

Johnson AL, Elwes RDC, Reynolds EH.
A three state model for analysing patterns of seizure control in epilepsy. Presented at the 17th Epilepsy International Conference, September 1987.

Joynt RJ.
The use of bromides for epilepsy.
Am J Dis Child 1974; 128:362-3

Juul-Jensen P.
Epilepsy. A clinical and social analysis of 1020 adult patients with epilepstic seizures.
Copenhagen: Munksgaard, 1963.

Juul-Jensen P.
Frequency of recurrence after discontinuance of anticonvulsant therapy in patients with epileptic seizures: a new follow-up study after 5 years.
Epilepsia 1968; 9:11-16.

Juul-Jensen P, Foldspang A.
Natural history of epileptic seizures.
Epilepsia 1983; 24:297-312.

Kaplan EL, Meier P.
Non parametric estimation from incomplete observations.
J Am Stat Assoc. 1958; 53;457-81.

Kimball OP
The treatment of epilepsy with sodium diphenyl-hydantoinate. JAMA 1939; 112:1244-5

Kiorboe E.
The prognosis of epilepsy.
Acta Psychiat et Neurol Scand. 1960; 36(suppl 150):166-78.

Kirstein L.
A contribution to the knowledge of the prognosis of epilepsy. Acta Med Scand 1942; 112:515-23.

Kuhl V, Kiorboe E, Lund M.
The prognosis of epilepsy with special reference to traffic security. Epilepsia 1967; 8:195-209.

Kurokawa T, Goya N, Fukuyama Y et al.
West syndrome and Lennox Gastaut syndrome: a survey of the natural history.
Pediatrics 1980; 65:81-88.

Kutt H, Haynes J, Mcdowell F.
Some causes of innefectiveness of diphenyl-hydantoin. Arch Neurol 1966; 14:489-92.

Lantville D, Loiseau P.
Evolution et pronostic de l'epilepsie chez l'enfant. Bordeau Med 1975; 8:2237-59.

Lennox WG.
Brain injury, drugs, and environment as causes of mental decay in epilepsy. Am J Psychiatr 1942; 99: 174-80.

Lennox WG.
The petit mal epilepsies. JAMA 1945; 129:1069-73.

Lennox WG, Davies JP.
Clinical correlates of the fast and slow spike-wave electroencephalogram.
Paediatrics. 1950: 5:626-44.

Lennox WG, Lennox MA.
Epilepsy and related disorders.
Boston: Little, Brown and Co., 1960.

Leppik IE, Cloyd J, Sanchuck R, Fryd D.
Coefficient of variance as an objective measure of compliance. In: Wada JA, Penry JK, eds. Advances in epileptology. New York, Raven Press; 1980:502-3.

Lerman P.
Benign partial epilepsy with with centro-temporal spikes. In: Roger J, Dravet C, Bureau M, Dreifuss FE, Wolf P,eds.Epileptic syndromes in infancy, childhood and adolescence. London: Libby, 1985.

Lerman P, Kivity S.
Benign focal epilepsy of childhood - a follow up study of 100 recovered patients.
Arch Neurol 1975; 32:261-4.

Lerman P, Kivity S.
Focal epileptic EEG discharges in children not suffering from clinical epilepsy: etiology, clinical significance and management. Epilepsia 1981; 22:551-558.

Lerman P, Kivity S.
Benign focal epilepsies of childhood. In: Pedley TA, Meldrum BS, eds. Recent advances in epilepsy, number three. Edinburgh: Churchill Livingstone 1986:137-156.

Lesser RP, Pippenger CE, Luders H, Dinner DS.
High dose monotherapy in treatment of intractable seizures. Neurology (Cleveland) 1984; 34:707-11.

Levy RH.
Variabillity in level-dose ratio of valproate: monotherpy versus polytherapy. Epilepsia 1984; 25 (suppl 1):S10-S13.

Lisk DR, Greene SH.
Drug compliance and seizure control in epileptic children. Postgrad Med J 1985; 61:401-5.

Livingston S.
Convulsive disorders in infants and children. Adv Paediatr. 1958; 10:113-95

Livingston S.
Comprehensive management of epilepsy in infancy, childhood and adolescence. Springfield, Illinois: CC Thomas, 1972.

Livingston S, Pearson PH.
Bromides in treatment of epilepsy. Am J Dis Child 1953; 86:717-20

Livingston S, Torres I, Pauli LL, Rider RV.
Petit mal epilepsy. Results of a prolonged follow-up study of 117 patients.
JAMA 1965; 194:113-8.

Loiseau P.
Rational use of valproate: Indications and drug regimen in epilepsy. Epilepsia 1984; 25(suppl 1): S65-S72.

Loiseau P.
Childhood abscence epilepsy. In: Roger J, Dravet C, Bureau M, Wolf P, eds. Epileptic syndromes in infancy, childhood and adolescence. London: John Libby, 1985:106-120.

Lombroso CT.
Sylvian seizures and mid-temporal spike foci in children. Archs Neurol 1967; 17:52-59

Lorge M.
Klinische erfahrungen mit einem nuen antiepileptic um, Tegretol (G 32883) mit besonderer nirkung auf die epileptische wesenveranderung.
Schweiz Med Wochenschr 1963; 93:1042-7.

Loiseau P, Pestre M, Dartigues JF et al.
Long-term progognosis in two forms of childhood epilepsy: typical abscence seizures and epilepsy with Rolandic(centrotemporal) EEG foci.
Ann Neurol 1983; 13:642-8.

Lund L, Jorgensen RS, Kuhl V.
Serum diphenylhydantoin (phenytoin) in ambulant patients with epilepsy. Epilepsia 1964; 5:51-8.

MaCardle B, McGowan MEL, Johnson AL, Neville BGR, Reynolds EH.
A comparitive monotherapy trial in childhood epilspey. Presented at the 17th Epilepsy Internat. Symposium, Jerusalem: 1987.

Maheshwari MC, Padmini R.
Role of carbamazepine in reducing polypharmacy in eilepsy. Acta Neurol Scand 1981; 64:22-8.

Maldonado A, Rangel R, Ramsay RE et al.
Prospective long-term outcome of patients with epilepsy. Presented at the Annual Meeting of the American Epilepsy Society. Baltimore, Md, 1987.

Mathai KV, Dunn DP, Kurland LT, Reeder FA.
Convulsive disorders in the Marina Islands.
Epilepsia 1968; 9:77-85.

Matsumoto A, Watanabe K, Negoro T et al.
Long term prognosis after infantilec spasms-a statistcal study of prognostic factors in 200 cases. Develop Med Child Neurol 1981; 23:51-65.

Mattson RH, Cramer JA, Collins JF et al.
Comparison of carbamazepine, phenobarbital, phenytoin and primidone in partial and secondarily generalised tonic clonic seizures.
N Engl J Med 1985; 313:145-51.

Meldrum BS.
Phamacological considerations in the search for new anticonvulsant drugs. In: Pedley TA, Meldrum BS, eds. Recent advances in epilepsy, number one. Edinburgh: Churchill Livingstone, 1983: 75-92

Merritt HH, Putnam TJ.
Sodium diphenylhydantoinate in the treatment of convulsive disorders. JAMA 1938; 111:1068-73.

Merritt HH, Putnam TJ, Schwab DH.
A new series of anticonvulsant drugs tested by experiments on animals. Arch Neurol Psychiat 1938; 39:1003-15.

Morikawa T, Osawa T, Ishihara O, Seito M.
A reppraisal of "benign epilepsy with centro-temporal foci". Brain Dev 1979; 1:275-285.

Naquet R, Soulayrol R, Dolce G et al.
First attempt at treatment of experimental status epilepticus and in animals and spontaneous status epilepticus in man with diazepam (valium). EEG Clin Neurophysiol 1965; 18:427.

Nayrac P, Beaussart M.
Les point-ondes prerolandiques expression EEG tres particuliere. Rev Neurol 1958; 99:201-6.

Nelson KB, Ellenberg JH.
Predictors of epilepsy in children who have experienced febrile seizures. N Engl J Med 1976; 295:1029-33.

Ohtahara S, Yamatogi Y, Ohtsuka Y, Oka E, Kanda S.
Prognosis in childhood epilepsy: a prospective follow-up study.
Folia Psychiatrica Neurologica Jap 1977; 31:301-13

Okuma T, Kumashiro H.
Natural history and prognosis of epilepsy: report of a multi-institutional study in Japan.
Epilepsia 1981; 22:35-53.

Oller-Daurella L.
Evolution et prognostic du syndrome de Lennox-Gastaut. In: Lugaresi E, Pazzaglia P, Tassinari CA, eds. Evolution and prognosis of epilepsies. Bologna: Aulo Gaggi, 1973:155-75.

Oller-Daurella L, Pamies R, Oller L.
Reduction or discontinuance of antiepileptic drugs in patients seizure-free for more than 5 years. In: Janz D, ed. Epileptology. Stuttgart: Theime, 1976:218-27.

Paskind HA, Brown M.
Frequency of seizures in epilepsy.
Arc Neurol Psychiat 1939; :65-8.

Penfield W, Erickson TC.
Epilepsy and cerebral localisation. Springfield-Baltimore: Thomas, 1941.

Perlstein MA.
Tridione: a new experimental drug for treatment of convulsive and related disorders. II, Clinical investigations Arch Neurol Psychiat 1946; 55:164-5.

Perrucha E.
Drug interactions. In: Laidlaw J, Richens A, eds. A textbook of epilepsy. Edinburgh 1982:358-71.

Peto R, Pike MC, Armitage NE et al.
Design and analysis of randomised clinical trials requiring prolonged observation of each patient.
Br J Cancer. 1977; 35:1-39.

Pollock LJ.
Remission of attacks in epilepsy treated with sodium bromide. JAMA 1938; 110:632-4

Probst C.
Uber den verlauf von hirnelektrisch stummen epilepsien. Schweiz Arch Neurol Psychiat 1960; 85:357-94.

Ramsay RE, Wilder BJ, Berger JR, Bruni J.
A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults.
Neurology (Cleveland) 1983; 33:904-10.

Rankin RM.
Prognosis of epilepsy in children.
Northwest Med 1972; 71:455-9.

Research Committee of the College of General Practitioners.
A survey of the epilepsies in general practice.
Br Med J 1960; 2:416-422

Reynolds EH.
Chronic antiepileptic Toxicity: a review.
Epilepsia. 1975; 16:319-52.

Reynolds EH.
Drug treatment of epilepsy.
Lancet 1978; 2:721-5.

Reynolds EH.
Serum levels of anticonvulsant drugs.
Interpretation and clinical value.
Pharmac Ther 1980; 8:217-35.

Reynolds EH.
Mental effects of antiepileptic medication: a review. Epilepsia 1983; 24(suppl 2):S85-95.

Reynolds EH.
The initiation of anticonvulsant drug therapy.
In: Pedley TA, Meldrum BS, eds. Recent advances in epilepsy, number two. Edinburgh: Churchill Livingstone, 1984:101-10.

Reynolds EH.
Early treatment and prognosis of epilepsy.
Epilepsia 1987; 28:97-106.

Reynolds EH, Chadwick D, Galbraith AW.
One drug (phenytoin) in the treatment of epilepsy.
Lancet 1976; i:923-6.

Reynolds EH, Elwes RDC, Shorvon SD.
Why does epilepsy become intractable? Prevention of chronic epilepsy.
Lancet. 1983; II:952-4.

Reynolds EH, Shorvon SD.
Monotherapy or polytherapy for epilepsy?
Epilepsia. 1981; 22:1-10.

Reynolds JR.
Epilepsy: Its symptoms, treatment, and relation to other chronic convulsive diseases. London 1861.

Richens A, Dunlop A.
Serum phenytoin levels in management of epilepsy.
Lancet 1975; ii:247-8.

Riikonen R.
A long term follow-up study of 214 children with the syndrome of infantile spasms.
Neuropedriatrics 1982; 13:14-23.

Robertson MM.
Current status of the 1,4- and 1,5- bezodiazepines in the treatment of epilepsy: the place of clobazam. Epilepsia 1986; 27(suppl 1):S27-S41

Rodin E.
The prognosis of patients with epilepsy.
Springfield Il: Charles C. Thomas, 1968

Rodin EA.
Medical and social prognosis in epilepsy.
Epilepsia 1972; 13:121-31.

Rodin E, Klutke G, Chayasirisobohn S.
Epileptic patients who are refractory to anti-convulsant medications. Neurology (NY) 1982; 32:1382-4.

Roger J, Dravet C, Bureau M, Dreifuss FE, Wolf P.
Epileptic syndromes in infancy childhood and adolescence. London: John Libby, 1985.

Roseman E.
Dilantin toxicity. A clinical and electro-encephalographic study. Neurology (NY) 1961; 11: 912 -21

Rowland LP.
Introduction to first annual Merritt-Putnam symposium, Cambridge.
Epilepsia. 1982; 23(suppl 1):S1-4.

Sander JWAS, Shorvon SD.
Incidence and prevalence studies in epilepsy and their metodoligcal problems: a review.
J Neurol Neurosurg Psychiatry 1987; 50:829-39.

Sauer H.
Uber gehauft kleine anfalle bei kindern (Pyknolepsie). Mschr Psychiatr Neurol 1960; 40: 276-300.

Saunders M, Marshall C.
Isolated seizures: an EEG and clinical assesment.
Epilepsa 1975; 16:731-3.

Schmidt D.
Reduction of two drug therapy in intractable epilepsy. Epilepsia 1983; 24:368-76.

Schmidt D, Tsai J-J, Janz D.
Generalised tonic-clonic seizures in patients with complex partial seizures: natural history and prognostic releveance. Epilepsia 1983; 24:43-8.

Schobben AFAM.
Pharmacokinetics and therapeutics in epilepsy.
Nijmegen: Stichting studentenpers, 1979:251-8.

Sherwin AL, Robb JP, Letcher M.
Improved control of epilepsy by monitoring plasma ethosuximide. Arch Neurol 1973; 28:178-81.

Shinnar S, Vining EPG, Mellits ED et al.
Discontinuing antiepileptic medication in children with epilepsy after two years without seizures. N Engl J Med 1985; 313:976-80.

Shope JT.
Medication Compliance. Pediatric Clinics of North America 1981; 28(1):5-21.

Shorvon SD
The temporal aspects of prognosis in epilepsy.
J Neurol Neurosurg Psychiatry 1984; 47:1157-65.

Shorvon S.
The treatment of epilepsy by drugs.
In: Hopkins A, ed. Epilepsy. London:
Chapman and Hall, 1987:229-82.

Shorvon SD, Chadwick D, Galbraith AW, Reynolds EH.
One drug for epilepsy.
Br Med J 1978; i:474-6.

Shorvon SD, Espir MLE, Steiner TJ, Dellaportas CI, Clifford Rose F.
Is there a place for placebo controlled trials of antiepileptic drugs? Br Med J 1985; 291:1328-9.

Shorvon SD, Johnson AL, Reynolds EH
Statistical and theoretical considerations in the design of anticonvulsant trials. In Dam M, Gram L, Penry JK, eds. The XIIth Epilepsy International Symposium. New York: Raven Press, 1981: 123-8

Shorvon SD, Reynolds EH.
Reduction in polypharmacy for epilepsy.
Br Med J 1979; 2:1023-5.

Shorvon SD, Reynolds EH.
Early prognosis of epilepsy.
Br Med J. 1982: 285:1699-701

Sieveking EH. .
Analysis of fifty-two cases of epilepsy observed by the author, Lancet 1857; 1:527-8.

Sillanpaa M.
Social functioning and seizure status of young adults with onset of epilepsy in childhood.
Acta Neurolog Scand 1983; 68 (suppl 96).

Smith JMB, Kellaway P.
Central (Rolandic) foci in children: an analysis of 200 cases. Electroenceph Clin Neurophysiol 1964; 17:460-1.

Sofijanov NG.
Clinical evolution and prognosis of childhood epilepsies. Epilepsia 1982; 23:61-9.

Strandjord RE, Johannessen SI. Carbamazepine as the only drug in patients with epilepsy: serum levels and clinical effect. In; Johannessen SI et al, eds. Antiepileptic therapy: advances in drug monitoring. New York: Raven Press, 1980:229-35.

Strobos RRJ
Prognosis in convulsive disorders.
Arc Neurol(Chic). 1959; 1:216-25

Tassinari CA, de Marco P.
Benign partial epilepsy with extreme sommato-sensory evokedpotentials. In: Roger J, Dravet C, Bureau M, Dreifuss FE, Wolf P, eds. Epileptic syndromes in infancy childhood and adolescence.

Temkin O.
The falling sickness. A history of epilepsy from the greeks to the beginnings of modern neurology. Second Edition, Revised. Baltimore: John Hopkins Press, 1971.

Theodore WH, Porter RJ.
Removal of sedative-hypnotic antiepileptic drugs from the regimens of patients with intractable epilepsy. Ann Neurol 1983; 13:320-4.

Thomas MH.
The single seizure- its study and managment.
JAMA 1959; 169:457-9.

Thompson PJ, Trimble MR.
Anticonvulsant drugs and cognitive function.
Epilepsia 1982; 23:531-44.

Thurston JH, Thurston DL, Hixon BB, Keller AJ.
Prognosis in childhood epilepsy: additional follow
-up of 148 children 15 to 23 years after with-
drawal of anticonvulsant therapy. N Eng J Med
1982; 306:831-6.

Todt H, Eysold R, Heduschke H-G, Vock K.
Klinische und electroenzephalographische
verlaufsbeobachtungen bei kindern nach einem
erstmaligen tonisch-klonischen anfall.
Z Klin Med 1985; 40:567-70.

Todt H.
The late prognosis of epilepsy in childhood:
results of a prospective follow-up study.
Epilepsia 1984; 25:137-44.

Trimble MR, Reynolds EH.
Anticonvulsants and mental symptoms: a review.
Psychological Medicine 1976; 6:169-78.

Trimble MR, Reynolds EH.
Neuropsychiatric toxicity of anticonvulsant drugs.
In: Matthews WG, Glaser GH, eds. Rcent advances in
clinical neurology, number four. Edinburgh:
Churchill Livingstone, 1984:261-280

Trimble MR, Thompson PJ.
Anticonvulsant drugs, cognitive function and
behaviour. Epilepsia 1983; 24(suppl 1):S55-S63

Trolle E.
Drug therapy of epilepsy. Acta Psychiat Scand
1960; 36(supl 150):187-99.

Troupin AS.
Carbamazepine re-examined. In: Pedley TA, Meldrum BS, eds. Recent advances in epilepsy, number one. Edinburgh: Churchill Livingstone, 1983:47-56.

Tucker SH, McJunkin JE.
Seizure recurrence.
N Engl J Med 1984; 311:1702.

Turnbull DM, Rawlins MD, Weightman D, Chadwick DW.
A comparison of phenytoin and valproate in previously untreated adult epileptic patients.
J Neurol Neurosurg Psychiat 1982; 45:55-9.

Turner WA.
Epilepsy, a study of the idiopathic disease.
London: Macmillan, 1907.

Van den Berg BJ, Yerushalmy J.
Studies on convulsive disorders in young children.
Pediat Res 1969; 3:298-304.

Van Heycop Ten Ham MW.
Complete recovery from epilepsy?
Huisants en Wetenshap 1980; 23:309-11.

Wallace SJ.
Febrile Convulsions. In: Hopkins A, ed. Epilepsy.
London: Chapman and Hall, 1987:443-67.

Wannamaker BB, Morton WA, Gross AJ, Saunders S.
Improvement in antiepileptic drug levels following reduction of intervals between clinic visits.
Epilepsia 1980; 21:155-62.

Wilks S.
Bromide and iodide of potassium in epilepsy. Cases and clinical remarks by Dr. Wilks. Medical Times and Gazette 1861; 2:635-6.

Williams D.
The borderlands of epilepsy revisited.
Brain 1975; 98:1-12.

Wolf P.
Epilepsy with grand mal on awakening. In: Roger J, Dravet C, Bureau M, Dreifuss FE, Wolf P, eds. Epileptic syndromes in infancy, childhood and adolescence. London: John Libby, 1985:259-70.

Yahr MD, Sciarra D, Carter S, Merritt HH.
Evaluation of standard anticonvulsant therapy in three hundred and nineteen patients.
JAMA 1952; 150:663-7.

Zenker C, Groh C, Roth G.
Probleme und erfahrungen beim absetzen anti-konvulsiver therapie. Z Kinderklinik 1957; 2: 152-63.

Zielinsky JJ.
Epidemiology. In: Laidlaw J. Richens A, eds. A Textbook of epilepsy.
Edinburgh: Churchill Livingstone, 1982: 16-33.

Zielinsky JJ.
People with epilepsy who do not consult physicians In: Janz D, ed. Epileptology. Stuttgart: George Thieme, 1976:18-23

Zimmermann FT
Use of methylphenylsuccimide in treatment of petit mal epilepsy. Arch Neurol Psychiat 1952; 66: 156-62

Zimmermann FT, Burgemeister BB.
A new drug for petit mal epilepsy.
Neurology 1958; 3:769-75.

APPENDICES

APPENDIX 1 DEMOGRAPHIC, CLINICAL AND FOLLOW-UP DETAILS RECORDED FOR PATIENTS ENTERING THE PILOT AND M.R.C. MONOTHERAPY TRIALS.

DEMOGRAPHIC DETAILS

- -Name:
- -Address:
- -General Practitioners Name and Address:
- -Hospital Number:
- -Date of Birth:
- -Occupation:
- -Source of Referall (GP or Casualty Officer):
- -Date of First Attendance:

SEIZURE HISTORY

- -Description of Seizures:
- -Classification of seizure/s:
  - Complex Partial Seizures
  - Simple Partial Seizures
  - Partial Seizures Secondarily Generalised
  - Tonic Clonic Seizures
  - Abscence Seizures
  - Atonic Seizures
  - Myoclnic Seizures
  - Others or unclassified
- -Dates of First and Subsequent Untreated Seizures:
- -Total Pretreatment Seizure Number:
- -Pretreatment Interval:
- -Timing of Seizures:
  - Nocturnal
  - Early Morning
  - Any Time
- -Precipitating Factors:
  - Alcohol
  - Sleep
  - Sress or Fatigue
  - Others/specify
- -Family History of Seizures:
  - Parents
  - Full Siblings
  - Children
  - Half Siblings
  - Grandparents
  - Aunts/Uncles
  - Cousins
- -Perinatal Complications:
- -Neonatal Seizures:

APPENDIX 1 contd.

DEVELOPMENTAL STATUS
- -Normal
- -Borderline
- -Delayed

MEDICAL HISTORY
- -Menningitis/Encephalitis
- -Head Injury requiring Hospital Stay of >48 hours or Loss of Consiousness >24 hours
- -Others

ASSOCIATED HANDICAPS
- -Psychiatric History
- -Social History

NEUROLOGICAL STATUS
- -Neurological Diagnoses
- -Neurological signs

INVESTIGATIONS
- -Routine Screening Bloods
  - FBC
  - Serum B12 and Folate and Red Cell Folate
  - SMAC Analysis
  - Serology
- -SXR
- -CT Brain Scan
- -Psychometry

FOLLOW UP DATA

- -Date of Clinic Visit
- -Number and Types of Seizures
  - Tonic Clonic
  - Partial
  - Absences
  - Myoclonic
  - Auras
- -Side Effects
  - Nystagmus
  - Ataxia
  - Lethargy
  - Rash
  - Gastrointestinal
  - Hirsuitism
  - Other
- -Anticonvulsants and Dosages
- -Investigations Performed

APPENDIX 2 ACTUARIAL ANALYSIS. COMPUTER PROGRAMME FOR DERIVATION OF SURVIVAL CURVES WRITTEN IN BASIC LANGUAGE.

The following parameters are used in the programme.

NUM = Total number of patients entering follow-up period
A(A) = Interval to event of interest, eg first seizure or remission
D(A) = Interval to end of follow-up
SFUW = Number of patients starting follow-up interval well
CPS = Cummulative probability of survival
LFU = Longest follow-up interval
EFU = number ending follow-up in interval "I"
AR = Number at risk
PD = Probability of dying
PS = Probability of surviving
CPS = Cumulative probability of surviving

APPENDIX 2 contd

```
10      PRINT "TOTAL NUMBER OF PATIENTS="
20      INPUT NUM
100     D$ = "": REM CTRL-D
120     PRINT D$"OPEN FILE"
130     PRINT D$"READ FILE"
133     DIM A(300)
134     DIM B(300)
135     DIM C(300)
136     DIM D(300)
137     DIM E(300)
138     DIM F(300)
139     DIM G(300)
140     DIM H(300)
141     DIM I(300)
142     DIM J(300)
143     DIM K(300)
144     DIM L(300)
145     DIM M(300)
146     DIM N(300)
147     DIM O(300)
148     DIM P(300)
149     DIM Q(300)
150     DIM R(300)
151     DIM S(300)
152     DIM T(300)
153     DIM U(300)
154     DIM V(300)
158     FOR A = 1 TO NUM
160     INPUT A(A),B(A),C(A),.....et seq
170     NEXT A
180     PRINT D$"CLOSE FILE"
410     SFUW = NUM
412     LOST = 0
420     CPS = 1
430     REM: SET DIM P(NUM) TO 0
450     FOR X = 1 TO NUM
460     P(X) = 0
470     NEXT X
500     REM: FIND LONGEST FOLLOW-UP
510     LFU = 0
520     FOR X = 1 TO NUM
530     IF D(X) > LFU THEN LFU = D(X)
540     NEXT X
600     REM: OPEN ACTUARIAL FOR INTERVALS 1 TO LFU
610     FOR I = 1 TO LFU
```

```
700     REM: MEASURE EFU FOR THIS INTERVAL
710     EFU = 0
720     FOR X = 1 TO NUM
722     IF P(X) = 1 GOTO 740 :REM DISCOUNT THOSE ALREADY
        DEAD
730     IF D(X) = I THEN EFU = EFU + 1
740     NEXT X
910     AR = SFUW - EFU/2
920     IF AR < 1 GOTO 1400
1000    REM: COUNT DYING
1004    DYING = 0
1010    FOR X = 1 TO NUM
1020    IF A(X) = I THEN DYING = DYING + 1
1030    NEXT X
1100    PD = DYING / AR
1120    PS = 1 - PD
1130    CPS = CPS * PS
1140    PRINT I,AR, ( INT (CPS*100))/100
1200    REM: CALCULATE SFUW FOR I +1
1210    REM: SET DIM P(X) TO 0 IF LOST
1220    LOST = DEAD OR EFU
1230    FOR X = 1 TO NUM
1240    IF A(X) = 1 THEN P(X) = 1
1250    IF D(X) = I THEN THEN P(X) = 1
1260    NEXT X
1300    LOST = 0
1310    FOR X 1 TO NUM
1320    IF P(X) = 1 THEN LOST = LOST + 1
1330    NEXT X
1340    SFUW = NUM - LOST
1350    NEXT I
1400    END
```

APPENDIX 3

CLINICAL CHARACTERISTICS OF 106 PATIENTS WITH NEWLY DIAGNOSED EPILEPSY

Characteristic	Legend number
1). Seizure type.	
Complex partial seizures.	1
Simple partial seizures.	2
Tonic clonic seizures.	3
2). Pre treatment tonic clonic seizure number.	
Two.	4
Three.	5
Four or more.	6
3). Pre treatment tonic clonic seizure frequency.	
High	7
Low.	8
4). Nocturnal seizures only.	9
5). Symptomatic epilepsy.	10
6). Neurological deficit	11
7) Familly hisory of epilepsy	12
8). Social Handicap	13
9). Psychiatric Handicap.	14
10). EEG Characteristics.	
Normal.	15
Minor slow wave changes.	16
Moderate or severe slow wave changes.	17
Epileptiform abnormalities.	18

x = present o = absent - = not applicable

Notes

i. Patient numbers 13, 44, 70 and 93 experinced partial seizures and a single secondarily generalised seizue.

ii. In patient number 28 the pretreatment tonic clonic seizure frequency was unknown.

Appendix 3 contd.

No.	Sex	Age	Legend number.																
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1	m	29	x	o	o	o	o	o	–	–	o	o	o	o	o	o	o	x	o	x
2	f	41	o	o	x	o	x	o	x	o	o	o	o	o	o	o	o	x	o	o	o
3	m	14	o	o	x	o	x	o	o	x	x	o	o	x	o	o	o	o	x	o
4	m	23	o	o	x	x	o	o	x	o	o	o	o	o	o	o	o	x	o	o
5	m	31	o	o	x	x	o	o	x	o	o	o	o	o	o	o	x	o	o	o
6	f	65	o	o	x	o	x	o	x	o	x	o	o	o	o	o	o	x	o	o
7	m	63	o	o	x	x	o	o	o	x	x	x	o	x	o	o	o	x	o	o
8	m	77	o	o	x	o	x	o	o	x	x	o	o	o	o	o	o	o	x	o
9	f	22	x	x	x	o	o	x	o	x	o	o	o	x	o	o	o	x	o	o
10	m	22	x	o	x	o	o	x	x	o	o	o	o	o	o	o	o	x	o	o
11	f	25	o	o	x	x	o	o	x	o	o	x	o	o	o	x	o	x	o	o
12	f	18	o	o	x	o	x	o	x	o	o	x	o	o	o	o	o	o	x	o
13	f	21	x	o	x	o	o	o	–	–	o	x	o	o	o	o	o	o	x	x
14	m	18	o	o	x	o	x	o	x	o	x	o	o	o	o	o	o	x	o	x
15	m	22	o	o	x	o	o	x	x	o	x	x	o	o	o	o	o	o	x	x
16	m	20	o	o	x	x	o	o	o	x	o	o	x	x	o	o	o	o	x	o
17	f	17	o	x	x	x	o	o	x	o	o	x	x	o	o	o	o	o	x	o
18	m	75	x	o	o	o	o	o	–	–	o	x	o	o	o	x	o	x	o	o
19	m	49	o	o	x	x	o	o	x	o	o	x	x	o	o	x	o	o	x	o
20	f	13	x	o	x	o	x	o	x	o	o	o	o	o	x	x	x	o	o	o
21	m	23	o	o	x	o	o	x	x	o	o	o	o	x	x	x	o	x	o	o
22	f	27	x	o	o	o	o	o	–	–	o	o	o	o	x	x	o	o	o	o
23	f	19	o	o	x	o	x	o	x	o	x	o	o	o	x	x	o	o	x	x
24	f	32	o	o	x	o	o	x	o	x	x	o	o	x	o	o	o	o	o	x
25	m	20	o	o	x	x	o	o	x	o	o	o	o	o	o	o	x	o	o	o
26	f	34	x	o	x	o	o	x	o	x	o	o	o	o	x	x	o	x	o	o
27	m	13	o	o	x	o	o	x	o	x	o	o	o	o	x	o	o	o	x	x
28	m	27	x	o	x	o	o	x	–	–	o	x	o	o	o	o	o	o	x	x
29	m	14	x	o	o	o	o	o	–	–	o	x	o	o	o	x	o	o	x	o
30	f	19	o	o	x	x	o	o	o	x	o	o	o	o	o	o	o	o	x	x
31	m	13	x	o	x	x	o	o	o	x	o	x	x	o	o	o	o	x	o	o
32	m	09	o	o	x	o	o	x	o	x	x	o	o	x	o	x	o	x	o	o
33	m	10	x	o	x	x	o	o	o	x	o	x	o	o	o	o	o	o	x	x
34	f	31	o	o	x	o	x	o	o	x	o	o	o	o	o	o	o	o	x	x
35	f	75	x	o	o	o	o	o	–	–	o	x	x	o	o	x	o	o	x	x
36	m	40	o	o	x	o	o	x	o	x	o	x	o	o	o	o	x	o	o	o
37	f	32	o	o	x	o	o	x	o	x	o	o	o	o	o	x	o	x	o	o
38	f	31	x	o	o	o	o	o	–	–	o	o	o	o	x	o	o	o	x	x
39	m	19	x	o	o	o	o	o	–	–	o	x	o	o	o	o	x	o	o	o
40	f	12	x	o	o	o	o	o	–	–	o	x	o	x	o	o	o	o	x	o
41	m	39	o	x	x	o	o	x	x	o	o	x	o	o	x	x	o	o	x	o
42	m	61	x	o	o	o	o	o	–	–	o	x	x	o	o	o	o	o	o	o
43	m	13	x	o	o	o	o	o	–	–	x	o	o	o	o	o	o	x	o	x
44	f	30	x	o	x	o	o	o	–	–	x	o	o	o	o	o	o	x	o	o
45	f	06	o	o	x	o	o	x	o	x	o	o	o	o	x	o	o	o	x	o
46	m	29	x	o	x	o	o	x	x	o	o	o	x	o	x	o	o	o	x	x
47	f	18	x	o	o	o	o	o	–	–	o	o	x	x	x	x	o	o	x	x
48	m	26	x	o	x	o	o	x	o	x	o	o	o	o	o	x	x	o	o	o

Appendix 3 contd.

No.	Sex	Age	Legend number.																
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
49	f	23	o	o	x	x	o	o	o	x	o	o	o	o	o	o	o	o	x	x
50	f	13	x	o	o	o	o	o	–	–	o	o	o	o	o	o	o	o	x	x
51	f	07	x	o	o	o	o	o	–	–	o	x	o	x	o	o	o	x	o	x
52	m	24	o	o	x	o	x	o	o	x	o	x	x	o	o	o	o	x	o	o
53	f	18	x	o	o	o	o	o	–	–	o	o	o	o	o	o	o	x	o	o
54	f	69	o	o	x	o	o	x	o	x	o	x	o	o	o	o	o	o	x	o
55	f	45	x	o	o	o	o	o	–	–	o	o	o	x	o	o	o	o	x	x
56	m	25	o	o	x	o	x	o	x	o	o	o	o	o	x	x	o	o	o	x
57	m	32	x	o	x	o	o	x	x	o	o	x	x	o	x	o	x	o	o	o
58	f	38	x	o	o	o	o	o	–	–	x	x	o	o	o	x	o	o	x	x
59	f	15	o	o	x	o	x	o	x	o	x	o	o	o	o	o	o	x	o	o
60	m	42	o	o	x	o	x	o	o	x	o	o	o	o	o	o	o	o	x	x
61	f	20	o	o	x	o	x	o	o	x	o	o	o	o	o	o	o	o	x	x
62	m	26	o	o	x	o	x	o	o	x	o	o	o	o	o	o	o	x	o	o
63	f	43	o	o	x	o	x	o	o	x	x	o	o	o	o	o	o	o	x	o
64	f	63	o	x	x	o	o	x	x	o	o	x	o	o	o	o	o	x	o	o
65	m	56	o	o	x	o	x	o	x	o	x	x	o	o	x	o	o	x	o	o
66	f	15	o	o	x	x	o	o	x	o	x	o	o	x	x	o	o	o	x	x
67	f	25	o	x	o	o	o	o	–	–	o	x	o	o	o	o	o	o	x	x
68	m	35	o	o	x	o	o	x	x	o	x	o	o	o	o	x	o	o	o	x
69	f	10	o	o	x	o	o	x	x	o	o	x	o	x	x	o	o	o	x	x
70	m	17	x	o	x	o	o	o	–	–	o	x	o	x	x	o	x	o	o	o
71	f	18	o	o	x	o	x	o	o	x	o	o	o	o	o	o	o	o	x	x
72	m	39	x	o	x	o	o	x	x	o	x	x	o	o	x	x	o	o	x	x
73	m	18	x	o	x	o	x	o	x	o	o	o	o	o	x	x	x	o	o	o
74	m	10	x	o	x	o	o	x	x	o	o	o	o	o	o	o	o	x	o	o
75	f	40	x	o	x	o	o	x	o	x	o	o	o	x	o	o	x	o	o	o
76	f	17	o	o	x	x	o	o	x	o	x	o	o	o	o	o	o	o	o	x
77	f	65	o	o	x	o	o	x	o	x	o	o	o	o	o	x	o	o	x	o
78	f	7	x	o	o	o	o	o	–	–	o	x	o	x	x	o	o	x	o	o
79	m	28	o	o	x	o	x	o	x	o	o	x	o	o	o	x	o	o	x	o
80	f	27	o	o	x	o	o	x	o	x	x	o	o	o	o	o	x	o	o	o
81	m	59	x	o	o	o	o	o	–	–	o	x	o	o	o	o	o	o	x	x
82	m	16	o	o	x	x	o	o	x	o	o	o	o	o	o	o	o	x	o	o
83	f	21	o	o	x	o	x	o	x	o	x	x	o	o	x	x	o	x	o	o
84	m	12	x	o	o	o	o	o	–	–	o	o	o	o	o	o	o	o	x	x
85	m	9	o	o	x	o	o	x	x	o	x	o	o	o	o	x	o	x	o	x
86	m	33	o	o	x	o	x	o	x	o	o	o	o	o	o	o	x	o	o	o
87	m	35	o	o	x	x	o	o	o	x	x	o	o	o	o	o	o	x	o	x
88	f	24	o	o	x	o	o	x	x	o	o	x	o	x	o	o	o	x	o	x
89	f	49	o	o	x	x	o	o	x	o	x	o	o	o	o	x	o	x	o	x
90	m	66	o	o	x	o	o	x	o	x	o	o	o	o	o	o	o	x	o	x
91	f	19	x	o	x	x	o	o	x	o	x	o	x	o	o	o	o	x	o	o
92	f	37	o	o	x	o	x	o	x	o	o	o	o	o	o	o	o	o	o	o
93	f	41	x	o	x	o	o	o	–	–	o	o	o	o	x	x	o	o	x	o
94	m	19	o	o	x	o	o	x	x	o	o	o	o	x	o	o	o	o	o	x
95	m	11	o	o	x	o	x	o	x	o	o	o	o	o	o	o	o	x	o	o
96	f	17	x	o	x	x	o	o	o	x	o	o	o	o	o	o	o	o	o	x
97	f	26	x	o	o	o	o	o	–	–	o	o	o	x	x	x	o	x	o	o

Appendix 3 contd.

No.	Sex	Age	Legend number.																
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
98	f	4	o	o	x	o	o	x	o	x	x	x	o	o	o	o	o	o	x	o
99	m	30	o	o	x	x	o	o	x	o	x	o	o	o	o	o	o	o	x	x
100	f	36	x	o	x	x	o	o	o	x	o	o	o	o	x	x	x	o	o	o
101	f	10	o	o	x	o	o	x	x	o	o	o	o	x	x	o	o	o	o	x
102	m	31	o	o	x	x	o	o	x	o	x	o	o	x	o	o	o	o	x	o
103	f	23	o	o	x	o	o	x	x	o	o	o	o	x	o	x	o	x	o	o
104	f	20	x	o	x	x	o	o	o	x	o	o	o	o	o	o	o	x	o	o
105	f	23	x	o	o	o	o	o	–	–	o	o	o	o	x	x	o	x	o	x
106	m	16	o	o	x	x	o	o	x	o	o	o	o	o	x	x	o	o	x	o

APPENDIX 4 THE PROGNOSIS FOR SEIZURE CONTROL IN 106 PATIENTS WITH NEWLY DIAGNOSED EPILEPSY. THE OCCURRENCE OF PARTIAL, TONIC CLONIC AND ALL SEIZURE TYPES BY EACH TWO MONTH PERIOD OF FOLLOW UP

Notes:

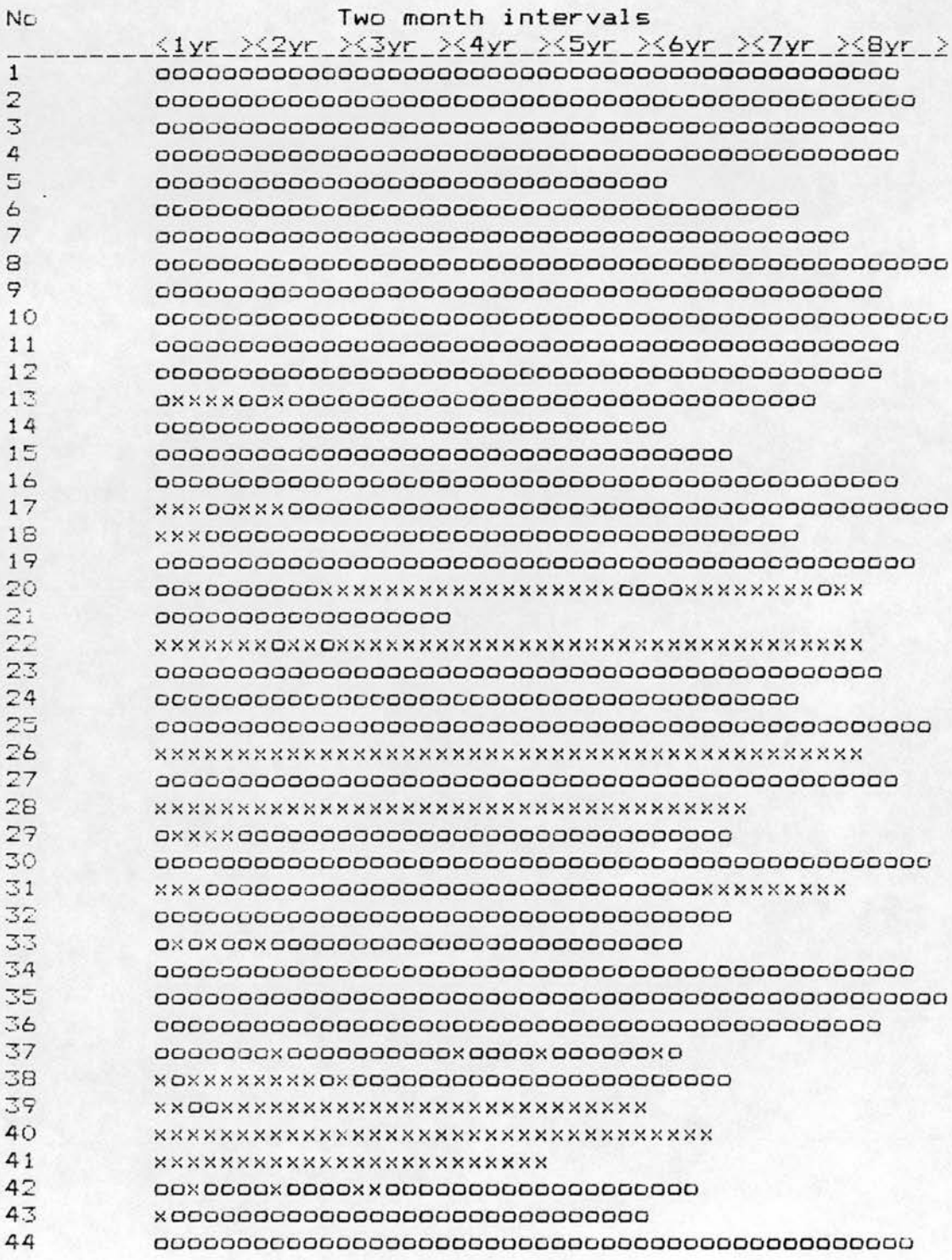
i. Each column relates to a two month interval of follow up.

o = no seizure occured
x = one or more seizures occured

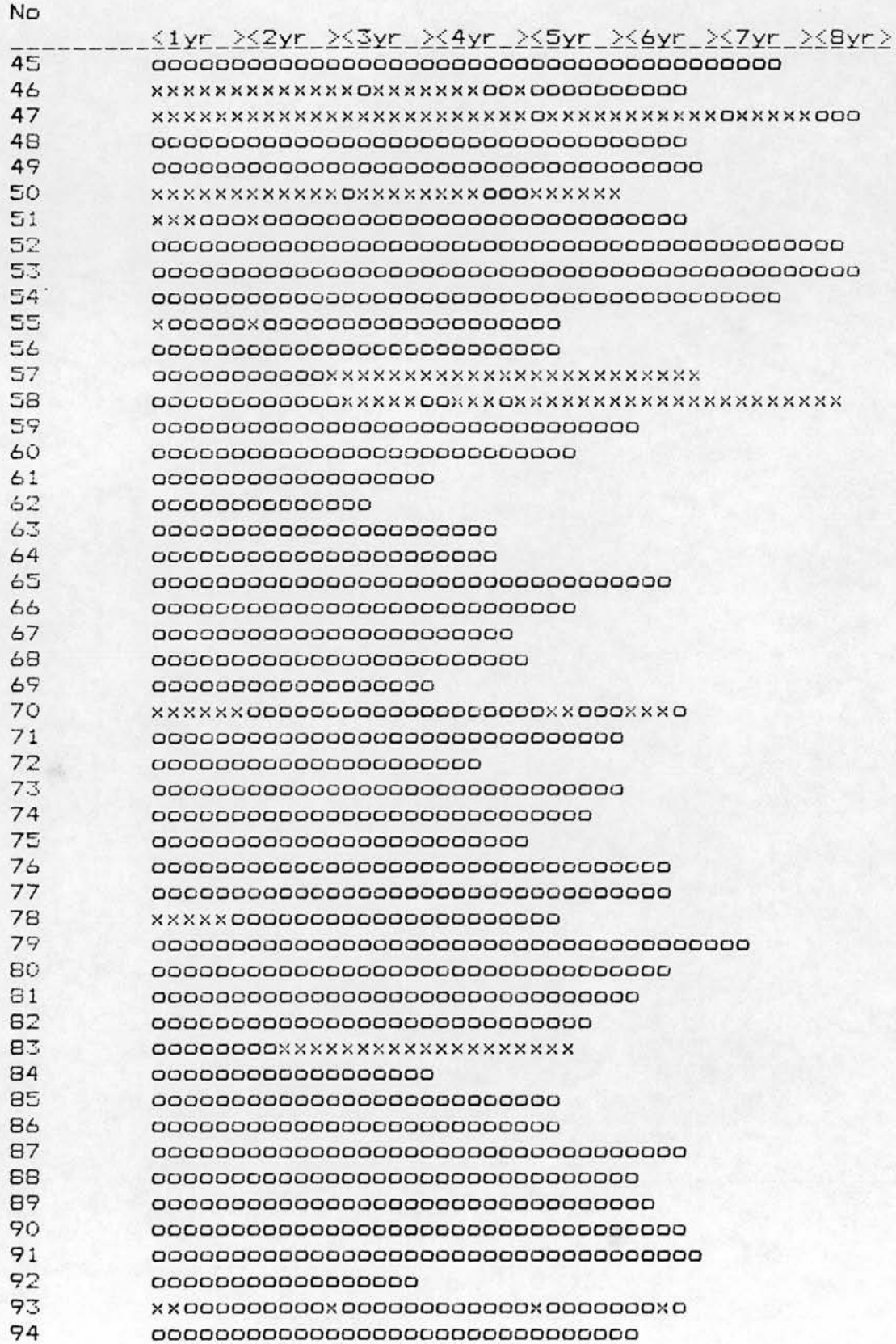
ii. Seizures that could be related directly to poor compliance have been excluded from the tables showing partial and tonic clonic seizures alone. In the final table showing all seizures combined those caused by poor compliance are marked by an asterix.

APPENDIX 4

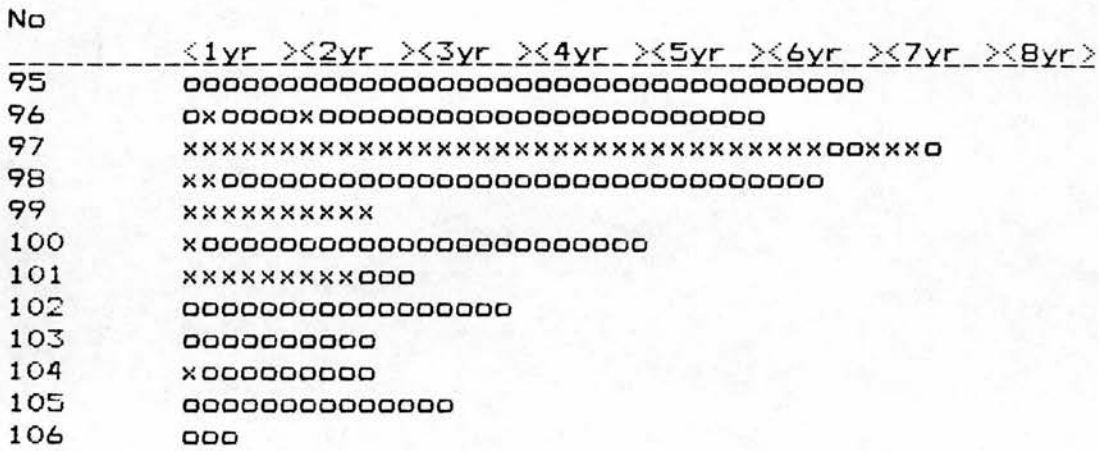
THE OCCURRENCE OF PARTIAL SEIZURES BY EACH TWO MONTH INTERVAL OF FOLLOW UP



APPENDIX 4, contd.

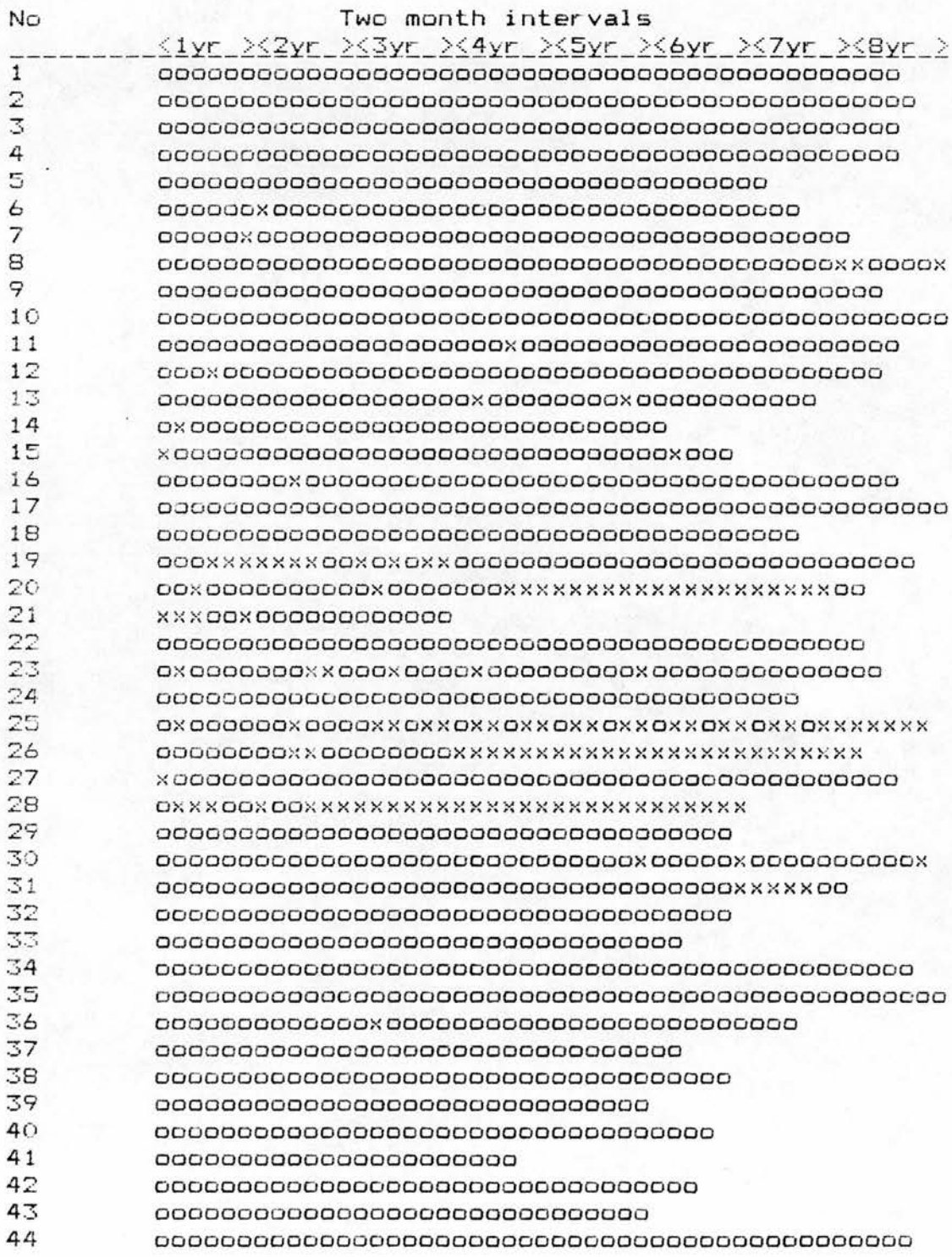


APPENDIX 4, contd.



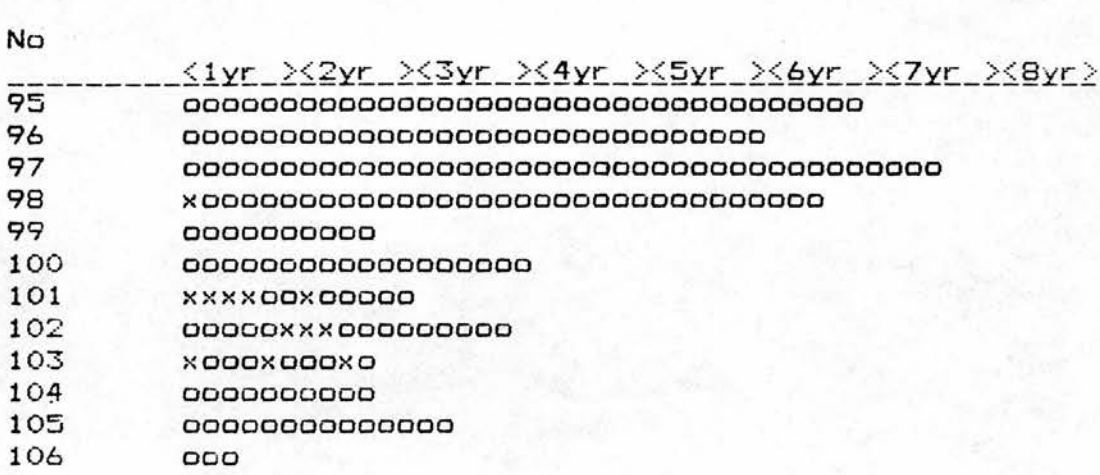
APPENDIX 4, contd.

THE OCCURRENCE OF TONIC CLONIC SEIZURES BY EACH TWO MONTH OF FOLLOW UP



APPENDIX 4, contd.

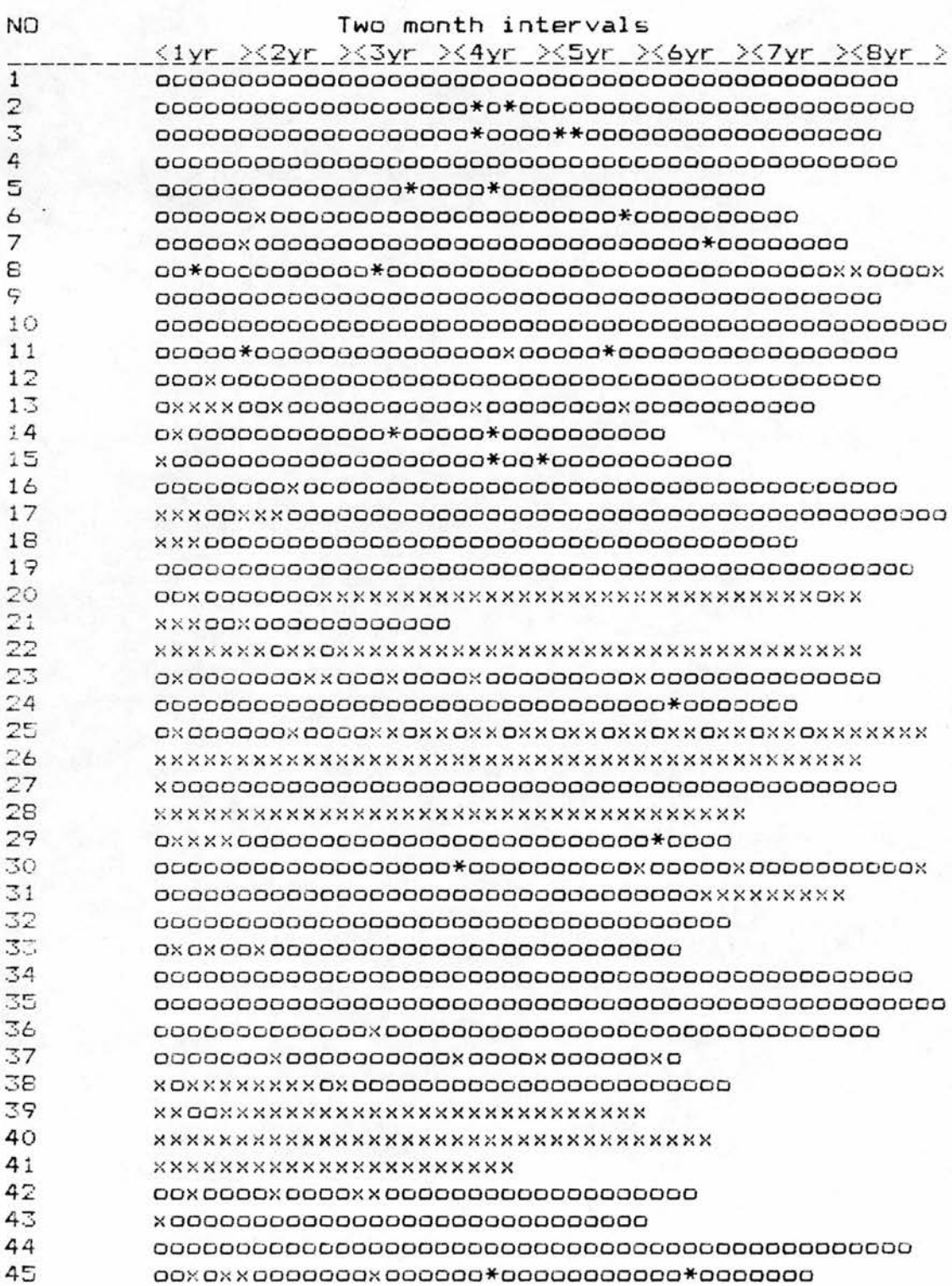
APPENDIX 4, contd.



APPENDIX 4, contd.

THE OCCURRENCE OF ALL SEIZURES BY TWO MONTH INTERVALS

OF FOLLOW UP



APPENDIX 4, contd.

APPENDIX 4, contd.

No

	<1yr ><2yr ><3yr ><4yr ><5yr ><6yr ><7yr ><8yr>
96	ox oooox ooooooooooo*ooooooooo
97	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxooxxxo
98	xxooooooooooooooooooooooooooooooooo
99	xxxxxxxxxx
100	xooooooooooooooooo
101	xxxxxxxxxooo
102	ooooaxxxooooooooo
103	xoooxoooxo
104	xoooooooo
105	ooooooooooooo
106	ooo

APPENDIX 5 CLINICAL CHARACTERISTICS AND FOLLOW-UP INTERVALS IN 214 PATIENTS WITH ONE OR MORE TONIC CLONIC SEIZURES

A. CLINICAL CHARACTERISTICS

	LEGEND	CODE
Symptomatic Seizures	1	
Nocturnal Seizures	2	
Family history of Epilepsy	3	x Present
Neurological Deficit	4	o Absent
EEG Characteristics		
Performed	5	
Normal	6	
Epileptic Abnormalities	7	
Non-specific Abnormalities	8	

B. NUMBER OF SEIZURES AT PRESENTATION, SEIZURE RECURRENCE AND FOLLOW-UP INTERVALS

Number of Seizures at Presentataion		
At First Ever Presentation	9	x One
At Neurology Outpatients Department	10	o More than one
Interval between first and second seizures (months)	11	
Interval between first seizure and first presentation (days)	12	
Interval between first seizure and presetation to neurology OPD (months)	13	
Interval between first seizure and end of follow-up (months)	14	

Patients treated following a first seizure: Nos. 18, 38, 60, 79, 88, 91, 93, 95, 98, 108, 112, 130, 136.

APPENDIX 5 contd.

No	Sex	Age	Legend number.													
			1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	f	10	o	o	o	o	x	x	o	o	x	x	17	1	1	19
2	m	57	o	o	o	o	x	o	o	x	x	x	0	1	1	1
3	f	13	o	o	o	o	x	o	o	x	x	x	7	1	2	32
4	f	38	o	o	o	o	x	x	o	o	x	x	12	11	2	26
5	f	26	o	o	o	o	x	x	o	o	x	o	2	1	3	19
6	f	16	o	x	o	o	x	x	o	o	x	o	1	4	1	46
7	f	11	o	o	o	o	x	o	x	x	x	x	28	48	2	46
8	m	52	x	o	o	x	o	o	o	o	x	o	1	1	2	13
9	f	45	x	o	o	o	x	x	o	o	x	x	3	1	1	9
10	m	20	o	o	o	o	x	o	o	x	x	x	19	1	1	39
11	m	14	o	o	o	o	x	o	x	x	x	o	1	1	1	19
12	m	15	o	o	o	o	x	o	o	x	x	x	2	1	1	33
13	f	48	o	o	o	o	o	o	o	o	x	o	2	1	2	23
14	m	14	x	o	o	o	x	o	o	x	x	o	1	1	3	8
15	f	44	o	o	o	o	x	x	o	o	x	x	52	1	3	54
16	f	17	o	o	o	o	o	o	o	o	x	x	9	1	1	16
17	f	13	o	o	o	o	x	x	o	o	x	o	5	1	5	16
18	f	4	o	o	o	o	x	o	o	x	x	x	7	1	2	16
19	f	16	x	x	o	x	x	x	o	o	x	x	3	1	1	6
20	m	6	o	x	o	o	x	o	x	o	x	x	5	1	4	7
21	m	10	o	o	o	o	x	o	o	x	x	x	4	1	2	4
22	f	11	o	o	x	o	x	o	o	x	x	o	1	1	1	25
23	m	11	o	o	o	o	x	o	o	x	x	o	1	1	1	14
24	f	10	o	o	o	o	x	o	x	x	x	x	3	1	1	34
25	f	15	o	x	o	o	o	o	o	o	x	x	8	1	1	31
26	m	25	o	o	x	o	x	o	o	x	x	x	3	1	1	12
27	m	37	o	o	o	o	x	x	o	o	x	o	9	1	9	16
28	f	25	x	o	o	x	x	x	o	o	x	x	3	1	2	20
29	m	28	x	x	o	x	x	x	o	o	x	o	2	1	2	16
30	f	16	o	o	o	o	x	x	o	o	x	o	1	7	2	9
31	m	18	o	o	x	o	x	x	o	o	x	x	17	1	2	20
32	f	20	o	o	o	o	x	x	o	o	x	x	0	1	1	15
33	m	22	o	o	o	o	o	o	o	o	x	x	0	1	1	1
34	f	17	o	o	o	o	x	x	o	o	x	x	23	2	1	23
35	f	43	o	o	o	o	x	o	o	x	x	x	0	1	3	51
36	m	20	o	o	x	o	x	o	o	x	x	x	0	1	3	4
37	m	33	o	o	o	o	x	o	o	x	x	x	0	8	2	3
38	m	29	o	x	o	o	o	o	o	o	x	x	0	1	1	2
39	m	49	o	o	o	o	x	o	o	x	x	x	0	1	1	3
40	m	15	o	x	o	o	x	x	o	o	x	o	1	1	1	13
41	m	12	x	o	o	o	x	x	o	o	x	x	5	1	2	60
42	m	38	o	o	o	o	x	o	o	x	x	x	0	1	1	15
43	f	20	o	o	o	o	x	o	x	x	x	x	0	4	2	45
44	m	13	o	x	o	o	o	o	o	o	x	x	0	1	1	15
45	m	15	o	o	x	o	x	o	o	x	x	x	0	16	2	10
46	f	51	o	o	o	o	x	o	x	o	x	x	0	1	1	5
47	m	33	o	o	o	o	x	o	o	x	x	x	0	10	5	7
48	m	25	o	o	o	o	x	x	o	o	x	x	0	1	2	40

APPENDIX 5 contd.

No	Sex	Age	Legend number.													
			1	2	3	4	5	6	7	8	9	10	11	12	13	14
49	m	25	x	o	o	o	x	o	o	x	x	x	7	2	1	58
50	m	34	x	o	o	o	x	o	o	x	x	x	4	14	2	7
51	m	24	o	o	o	o	x	o	o	x	x	x	0	1	2	3
52	f	29	o	o	o	o	x	o	o	x	x	x	0	1	6	7
53	m	17	o	o	o	o	x	o	o	x	x	x	0	1	1	31
54	f	38	x	x	o	o	o	o	o	o	x	x	0	4	3	32
55	f	38	o	o	o	o	x	x	o	o	x	x	0	1	1	20
56	m	21	o	o	o	o	x	x	o	o	x	x	0	1	1	7
57	m	18	o	o	o	o	x	o	x	o	x	x	6	1	2	36
58	f	18	o	o	o	o	x	o	x	o	x	x	0	1	1	4
59	m	45	o	o	o	o	x	x	o	o	x	x	0	1	2	2
60	f	21	o	o	o	o	o	o	o	o	x	x	0	1	2	2
61	f	40	o	o	o	o	x	x	o	o	x	o	1	1	2	3
62	f	21	o	x	o	o	x	x	o	o	x	o	1	1	3	3
63	f	22	o	o	o	o	x	o	o	x	x	x	5	4	1	18
64	m	29	o	o	o	o	x	o	o	x	x	o	1	1	1	65
65	f	30	o	x	o	o	x	x	o	o	x	o	1	3	4	14
66	m	13	o	o	o	o	o	o	o	o	x	o	6	1	6	10
67	f	2	o	x	o	o	o	o	o	o	x	o	6	1	45	54
68	f	11	o	o	o	o	x	o	x	o	x	x	2	1	1	24
69	f	5	o	o	o	o	x	o	o	x	x	x	11	1	5	45
70	m	19	x	o	x	x	x	x	o	o	x	o	1	2	3	11
71	m	69	x	x	o	o	x	x	o	o	x	o	10	1	12	55
72	m	52	x	o	o	o	o	o	o	o	x	o	1	1	1	1
73	f	17	o	o	o	o	x	o	o	x	x	o	1	1	1	9
74	m	23	o	o	o	o	x	o	x	x	x	o	1	1	1	8
75	m	38	o	x	o	o	x	x	o	o	x	x	11	1	1	18
76	m	17	o	o	o	o	x	o	o	x	x	o	1	1	7	9
77	m	33	o	o	o	o	o	o	o	o	x	o	7	1	12	34
78	m	36	o	x	o	o	o	o	o	o	x	x	8	1	1	11
79	m	4	o	x	o	o	o	o	o	o	x	x	0	1	1	7
80	m	6	o	o	o	o	x	x	o	o	x	x	5	1	4	39
81	f	64	o	o	o	o	x	o	o	x	x	x	5	1	1	13
82	m	15	o	o	x	o	x	o	o	x	x	o	2	1	3	11
83	m	19	o	o	o	o	x	x	o	o	x	o	1	1	4	4
84	m	64	x	o	o	x	o	o	o	o	x	x	2	1	1	9
85	m	16	o	o	o	o	x	x	o	o	x	x	0	1	2	3
86	f	62	o	o	o	o	o	o	o	o	x	x	0	1	1	12
87	f	20	o	x	o	o	x	o	x	o	x	x	0	1	1	12
88	m	66	x	o	o	x	x	x	o	o	x	x	0	1	1	13
89	m	55	o	o	o	o	o	o	o	o	x	o	1	1	3	47
90	m	13	o	o	o	o	x	x	o	o	x	x	6	1	1	7
91	f	22	o	o	o	o	o	o	o	o	x	x	0	1	2	8
92	m	30	o	o	o	o	o	o	o	o	x	o	1	1	1	2
93	m	15	x	o	o	x	x	o	x	o	x	o	2	1	2	4
94	m	40	o	o	o	o	x	o	x	o	x	o	1	1	1	6
95	m	35	o	o	o	o	x	o	o	x	x	x	0	1	2	3
96	f	42	o	o	o	o	o	o	o	o	x	x	13	1	1	15

APPENDX 5 contd.

No	Sex	Age	Legend number.													
			1	2	3	4	5	6	7	8	9	10	11	12	13	14
97	f	24	o	o	o	o	x	x	o	o	x	x	0	1	1	2
98	m	30	x	o	o	x	o	o	o	o	x	x	0	1	3	5
99	f	38	o	o	o	o	o	o	o	o	x	x	0	1	1	6
100	f	19	o	o	o	o	o	o	o	o	x	x	0	9	2	2
101	m	12	o	o	x	o	x	o	x	o	x	x	0	3	1	21
102	f	64	o	o	o	o	o	o	o	o	x	o	6	1	6	22
103	m	18	o	o	o	o	x	o	x	x	x	o	1	1	7	9
104	f	15	o	x	o	o	x	x	o	o	x	x	0	1	2	20
105	m	17	o	o	o	o	x	x	o	o	x	x	0	1	1	5
106	f	23	o	x	o	o	x	o	x	o	x	x	0	1	1	64
107	m	21	o	o	o	o	o	o	o	o	x	x	0	1	3	31
108	f	13	o	o	o	o	x	o	o	x	x	x	6	1	2	29
109	f	78	x	o	o	x	x	o	x	x	x	x	0	1	6	18
110	f	19	o	o	o	o	x	x	o	o	x	x	0	1	1	63
111	m	6	o	x	o	o	x	x	o	o	x	o	5	1	7	36
112	m	24	o	o	o	o	x	o	x	x	x	x	0	1	1	50
113	m	24	o	x	o	o	o	o	o	o	x	x	0	5	3	18
114	f	38	o	x	o	o	o	o	o	o	x	x	0	1	1	1
115	f	17	o	o	o	o	x	o	o	x	x	x	0	1	1	69
116	m	11	o	o	o	o	x	x	o	o	x	x	0	1	1	26
117	f	12	o	x	o	o	x	o	x	o	x	o	2	1	2	47
118	m	14	o	o	x	o	x	x	o	o	x	x	0	2	2	5
119	m	17	o	o	o	o	x	x	o	o	x	x	0	1	1	4
120	f	7	o	o	o	o	x	o	o	x	x	x	0	1	3	7
121	m	15	o	o	o	o	x	o	x	o	x	x	0	1	2	31
122	f	31	o	o	o	o	x	o	x	o	x	x	0	1	1	3
123	m	22	o	x	o	o	x	o	x	o	x	x	0	1	1	4
124	f	11	o	x	o	o	x	o	x	o	x	o	9	1	15	49
125	f	55	x	x	o	o	o	o	o	o	x	o	1	1	3	1
126	f	37	o	o	o	o	x	o	o	x	x	x	8	1	2	53
127	m	51	o	o	o	o	x	x	o	o	x	o	2	1	2	41
128	f	25	o	o	o	x	x	o	x	o	x	x	0	6	4	47
129	f	40	x	o	o	x	x	o	o	x	x	x	0	1	1	14
130	m	17	o	o	o	o	x	o	x	x	x	x	24	1	1	24
131	m	8	o	x	o	o	x	o	x	o	x	x	10	1	5	35
132	m	57	o	x	o	o	x	x	o	o	x	x	6	1	2	47
133	m	30	o	o	o	o	o	o	o	o	x	x	0	1	1	49
134	m	64	o	o	o	o	x	x	o	o	x	x	0	1	2	18
135	f	24	o	o	o	o	x	x	o	o	x	x	0	1	2	2
136	m	3	o	o	o	o	o	o	o	o	x	o	1	1	3	3
137	f	20	o	o	o	o	x	x	o	o	x	x	0	7	2	20
138	m	15	o	o	o	o	x	x	o	o	x	x	0	6	3	6
139	f	22	o	o	o	o	x	x	o	o	x	x	8	1	1	28
140	m	15	o	o	x	o	x	o	o	x	x	o	2	1	2	8
141	f	22	o	o	x	o	x	o	o	x	x	x	0	1	4	48
142	f	17	o	o	o	o	x	o	x	x	x	x	0	1	1	9
143	m	52	o	o	x	o	x	x	o	o	x	o	1	1	1	13
144	f	31	o	x	o	o	x	x	o	o	x	x	0	1	1	25

APPENDIX 5 contd.

No	Sex	Age	Legend number. 1	2	3	4	5	6	7	8	9	10	11	12	13	14
145	m	74	o	o	o	x	x	o	o	x	x	x	0	1	1	5
146	f	65	o	o	o	o	x	o	o	x	x	o	1	1	2	2
147	f	20	o	o	x	o	x	o	x	o	o	o	75	-	154	171
148	m	43	o	o	o	o	x	o	o	x	o	o	-	-	120	132
149	f	21	o	o	o	o	x	o	x	o	o	o	-	-	120	144
150	f	17	o	o	o	o	x	x	o	o	o	o	7	-	9	9
151	m	16	x	o	o	x	x	x	o	o	o	o	4	-	7	22
152	m	11	o	o	x	x	x	o	o	x	o	o	60	-	60	96
153	f	33	o	o	o	o	o	o	o	o	o	o	-	-	4	36
154	f	24	o	x	o	o	x	o	o	x	o	o	1	-	4	25
155	m	19	o	o	o	x	x	o	o	x	o	o	2	-	2	23
156	m	34	o	o	o	o	x	o	o	x	o	o	1	-	1	40
157	f	18	o	x	o	x	x	o	o	x	o	o	1	-	6	19
158	m	17	o	o	o	o	x	o	x	x	o	o	-	-	3	10
159	m	3	o	o	o	o	x	x	o	o	o	o	1	-	2	18
160	f	6	o	o	x	o	x	o	o	x	o	o	9	-	7	55
161	m	13	o	o	o	o	x	o	x	o	o	o	1	-	2	33
162	f	8	o	o	o	o	x	o	o	x	o	o	-	-	48	84
163	m	11	o	o	o	o	x	o	x	x	o	o	12	-	13	46
164	f	2	o	o	o	o	x	o	x	o	o	o	1	-	2	34
165	m	8	o	o	o	o	x	o	x	x	o	o	7	-	13	42
166	m	59	o	o	o	o	o	o	o	o	o	o	3	-	3	26
167	f	7	o	o	o	o	x	o	x	o	o	o	1	-	1	9
168	f	2	o	x	x	o	x	o	x	o	o	o	-	-	-	-
169	f	14	x	o	x	o	o	o	o	o	o	o	3	-	5	37
170	f	12	o	o	o	o	x	o	x	o	o	o	1	-	2	28
171	f	12	o	o	o	x	x	o	o	x	o	o	-	-	3	36
172	f	9	x	o	o	o	x	o	o	x	o	o	-	-	5	23
173	m	25	o	o	o	o	x	x	o	o	o	o	1	-	1	4
174	m	65	o	x	o	o	x	o	o	x	o	o	-	-	5	25
175	m	5	o	o	o	o	x	o	x	x	o	o	1	-	2	26
176	m	11	o	o	o	o	x	o	x	x	o	o	4	-	1	47
177	m	82	o	x	o	o	o	o	o	o	o	o	-	-	4	15
178	m	37	o	o	o	o	o	o	o	o	o	o	2	-	3	5
179	f	69	o	o	o	x	x	x	o	o	o	o	-	-	6	15
180	f	56	o	o	o	o	x	o	o	x	o	o	-	-	-	-
181	f	11	o	o	o	o	o	o	o	o	o	o	-	-	-	-
182	f	18	o	o	o	o	x	o	o	x	o	o	1	-	2	47
183	m	30	o	o	o	o	o	o	o	o	o	o	1	-	1	1
184	f	38	o	o	o	o	o	o	o	o	o	o	-	-	-	-
185	m	17	o	o	o	o	x	x	o	o	o	o	-	-	4	34
186	f	41	o	x	o	o	o	o	o	o	o	o	1	-	1	74
187	f	16	o	o	o	o	o	o	o	o	o	o	-	-	2	50
188	f	20	o	o	x	o	o	o	o	o	o	o	3	-	4	22
189	f	59	o	o	o	o	x	o	o	x	o	o	1	-	1	31
190	m	24	o	o	o	o	x	x	o	o	o	o	-	-	60	120
191	m	21	o	o	o	o	x	o	o	x	o	o	-	-	-	-
192	f	18	o	o	o	o	x	o	x	x	o	o	48	-	48	91
193	m	9	x	o	o	x	x	o	x	o	o	o	24	-	24	33

APPENDIX 5 contd.

No	Sex	Age	Legend number.													
			1	2	3	4	5	6	7	8	9	10	11	12	13	14
194	m	13	x	o	o	o	x	o	x	x	o	o	60	-	67	84
195	m	18	o	o	o	o	x	o	o	x	o	o	4	-	55	65
196	f	31	x	o	x	o	x	o	x	o	o	o	75	-	118	147
197	f	54	x	x	o	o	x	o	o	x	o	o	48	-	56	67
198	m	20	o	o	o	o	o	o	o	o	o	o	96	-	96	104
199	f	12	o	o	o	o	x	o	x	o	o	o	24	-	25	48
200	f	28	x	x	o	o	x	x	o	o	o	o	204	-	204	228
201	f	19	o	o	o	o	x	x	o	o	o	o	48	-	52	79
202	m	16	o	o	o	o	x	o	x	x	o	o	72	-	72	105
203	m	25	o	x	o	o	x	o	o	x	o	o	24	-	25	27
204	m	24	o	o	o	o	x	x	o	o	o	o	156	-	157	169
205	m	16	o	o	o	x	x	o	x	x	o	o	60	-	60	87
206	m	27	o	x	o	o	x	x	o	o	o	o	72	-	60	144
207	f	12	o	x	o	o	x	x	o	o	o	o	132	-	132	144
208	m	51	o	o	o	o	x	x	o	o	o	o	37	-	39	86
209	m	44	x	o	o	o	x	o	x	x	o	o	192	-	192	197
210	f	20	o	x	o	o	x	o	o	x	o	o	24	-	36	67
211	f	33	o	o	o	o	x	o	o	x	o	o	132	-	132	182
212	f	17	x	x	o	x	o	o	o	x	o	o	96	-	96	132
213	f	14	o	o	x	o	o	o	o	o	o	o	24	-	24	24
214	m	44	o	o	o	o	x	x	o	o	o	o	-	-	-	-

APPENDIX 6 CLINICAL CHARACTERISTICS AND FOLLOW-UP INTERVALS IN 183 PATIENTS WITH UNTREATED TONIC CLONIC SEIZURES

A. CLINICAL CHARACTERISTICS

	LEGEND	CODE	
Neurological Deficit	1	x	Present
		o	Absent
Symptomatic Seizures	2	x	Present
		o	Absent
Pretreatment Seizure Number	3	n	Number of Seizures
		0	Untreated
		–	Unknown
Pretreatment Interval	4	n	Interval, Months
		0	Untreated
		–	Unknown
Interval, Seizure 1 to 2	5	n	Interval, Weeks
		–	Unknown
Interval, Seizure 2 to 3	6	n	Interval, Weeks
		0	No Seizure
		–	Unknown
Interval, Seizure 3 to 4	7	n	Interval, Weeks
		0	No Seizure
		–	Unknown
Interval, Seizure 4 to 5	8	n	Interval, Weeks
		0	No Seizure
		–	Unknown

B. FOLLOW UP ON TREATMENT

Time to First Seizure	9	n	Interval, Months
		x	Not Treated
		–	Unknown
Time to First 1 Year Remission	10	n	Interval, Months
		x	Not Treated
		–	Unknown
Duration of Follow-up	11	n	Interval, Months
		x	Not Treated
		–	Unknown

APPENDIX 6 contd.

No	Sex	Age	Legend number.										
			1	2	3	4	5	6	7	8	9	10	11
1	m	35	o	o	2	2	5	0	0	0	7	21	72
2	f	59	o	o	2	1	1	0	0	0	1	22	30
3	f	12	o	o	2	1	2	0	0	0	40	12	47
4	m	6	o	o	2	2	4	0	0	0	11	24	30
5	m	18	o	o	2	35	18	0	0	0	x	x	x
6	f	14	o	o	2	38	152	0	0	0	x	x	x
7	m	25	o	x	2	58	28	0	0	0	x	x	x
8	m	7	o	o	2	24	96	0	0	0	x	x	x
9	m	65	o	x	2	6	24	0	0	0	-	-	-
10	m	14	o	o	2	6	24	0	0	0	-	-	-
11	f	17	o	o	2	23	92	0	0	0	x	x	x
12	m	18	o	o	2	8	20	0	0	0	0	0	0
13	f	16	o	o	2	9	2	0	0	0	0	0	9
14	f	46	o	o	2	40	160	0	0	0	0	0	2
15	m	14	o	o	3	10	8	32	0	0	x	x	x
16	f	56	o	o	2	2	7	0	0	0	1	0	9
17	m	15	o	o	2	2	8	0	0	0	3	0	31
18	f	12	o	o	3	31	96	24	0	0	3	15	17
19	m	14	o	o	2	1	1	0	0	0	10	0	21
20	f	28	o	x	2	8	28	0	0	0	2	0	15
21	m	20	o	o	2	26	76	0	0	0	-	-	-
22	f	45	o	x	2	6	12	0	0	0	-	-	-
23	m	52	x	x	2	2	4	0	0	0	-	-	-
24	f	11	o	o	2	30	120	0	0	0	-	-	-
25	f	19	o	o	2	48	192	0	0	0	-	-	-
26	m	16	o	o	3	76	288	16	0	0	-	-	-
27	f	26	o	o	2	1	4	0	0	0	-	-	-
28	f	38	o	o	2	11	44	0	0	0	-	-	-
29	f	13	o	o	2	32	26	0	0	0	-	-	-
30	f	10	o	o	2	19	68	0	0	0	x	x	x
31	m	25	o	o	2	24	96	0	0	0	0	0	3
32	f	65	o	o	2	2	3	0	0	0	x	x	x
33	m	53	o	o	2	1	1	0	0	0	x	x	x
34	f	25	o	o	3	10	32	8	0	0	0	12	19
35	m	8	o	o	12	18	42	4	20	4	x	x	x
36	f	47	o	o	2	8	30	0	0	0	22	12	46
37	f	12	o	o	2	11	2	0	0	0	6	0	36
38	m	42	o	o	2	15	52	0	0	0	x	x	x
39	m	40	o	o	2	4	4	0	0	0	x	x	x
40	m	15	x	o	2	4	5	0	0	0	x	x	x
41	m	13	o	o	2	6	22	0	0	0	2	0	2
42	m	54	o	o	3	3	4	4	0	0	-	-	-
43	m	66	x	x	2	3	12	0	0	0	0	0	8
44	f	20	o	o	3	96	336	32	0	0	6	0	44
45	f	26	o	o	2	3	1	0	0	0	0	0	0
46	f	22	o	o	3	24	56	20	0	0	0	0	8
47	m	15	o	o	2	3	9	0	0	0	5	0	6
48	m	69	o	o	3	14	40	16	0	0	-	-	-

APPENDIX 6 contd.

No	Sex	Age	Legend number.										
			1	2	3	4	5	6	7	8	9	10	12
49	m	52	o	x	2	1	2	0	0	0	x	x	x
50	f	17	o	o	2	1	1	0	0	0	3	o	9
51	m	23	o	o	3	5	5	13	0	0	0	o	4
52	m	14	o	o	2	36	6	0	0	0	x	x	x
53	f	41	o	o	3	6	12	12	0	0	39	12	91
54	m	14	o	o	3	8	12	16	0	0	39	12	89
55	m	23	o	o	2	2	4	0	0	0	0	12	89
56	m	31	o	o	2	3	4	0	0	0	31	12	73
57	f	65	o	o	3	3	4	4	0	0	13	12	77
58	m	63	o	x	2	12	20	0	0	0	11	25	83
59	m	77	o	o	3	20	48	32	0	0	5	17	95
60	m	20	x	o	2	5	8	0	0	0	17	12	89
61	m	49	x	x	2	3	12	0	0	0	0	12	91
62	f	13	o	o	3	4	12	4	0	0	5	0	85
63	f	19	o	o	2	12	48	0	0	0	37	12	93
64	m	10	o	x	2	12	36	0	0	0	3	25	63
65	m	29	x	o	4	2	2	4	2	0	1	59	67
66	f	23	o	o	2	5	20	0	0	0	3	21	71
67	f	20	o	o	2	2	1	0	0	0	1	13	19
68	m	25	o	o	3	4	4	12	0	0	0	41	53
69	f	15	o	o	3	6	4	4	0	0	0	12	61
70	f	15	o	o	2	4	16	0	0	0	7	25	53
71	m	35	o	o	4	4	4	4	4	0	1	23	47
72	f	17	o	o	2	3	4	0	0	0	0	12	65
73	m	16	o	o	2	4	16	0	0	0	3	19	53
74	m	33	o	o	3	6	8	16	0	0	0	12	49
75	m	35	o	o	2	18	16	0	0	0	0	12	65
76	f	49	o	o	2	1	4	0	0	0	1	23	61
77	f	19	x	o	2	4	4	0	0	0	0	12	67
78	f	37	o	o	3	4	12	4	0	0	7	19	33
79	m	11	o	o	3	5	12	8	0	0	39	12	68
80	f	17	o	o	2	8	24	0	0	0	3	27	59
81	m	35	o	o	3	1	3	1	0	0	5	37	40
82	f	15	o	o	3	12	28	8	0	0	7	0	27
83	m	25	o	o	2	3	11	0	0	0	24	12	31
84	m	11	x	o	2	60	240	0	0	0	0	12	28
85	m	17	x	o	2	8	16	0	0	0	27	12	30
86	m	16	o	o	3	12	24	8	0	0	0	12	17
87	m	16	o	o	2	10	34	0	0	0	2	16	25
88	f	18	o	o	4	45	101	40	28	0	0	12	19
89	m	18	x	o	2	4	12	0	0	0	0	12	22
90	m	32	o	o	2	11	28	0	0	0	9	0	20
91	m	36	x	o	2	2	7	0	0	0	0	12	21
92	m	29	o	o	2	9	36	0	0	0	0	0	9
93	f	20	o	o	3	9	24	12	0	0	x	x	x
94	m	13	o	o	4	57	16	100	108	0	6	18	20
95	m	19	x	o	4	4	4	4	4	0	10	0	19
96	m	40	o	o	2	1	1	0	0	0	1	0	4

APPENDIX 6 contd.

No	Sex	Age	Legend number.										
			1	2	3	4	5	6	7	8	9	10	12
97	f	20	o	o	5	132	75	64	152	5	7	0	13
98	m	35	o	o	4	15	36	16	8	0	0	12	13
99	m	36	o	o	2	7	25	0	0	0	11	0	12
100	f	17	o	o	6	20	52	8	2	3	6	0	11
101	f	18	o	o	5	9	4	20	3	2	7	0	12
102	m	17	o	x	3	10	4	28	0	0	2	0	8
103	f	57	o	o	4	18	24	20	24	0	0	0	10
104	m	38	o	o	4	16	48	8	8	0	0	0	10
105	m	31	o	o	2	1	1	0	0	0	0	0	0
106	m	27	o	o	3	42	140	8	0	0	1	0	1
107	f	18	o	o	4	12	40	4	2	0	0	0	8
108	m	24	o	o	2	6	4	0	0	0	x	x	x
109	f	23	o	o	3	5	3	16	0	0	0	0	0
110	m	14	o	x	3	36	72	24	0	0	0	0	0
111	m	28	o	o	4	7	4	16	4	0	1	0	2
112	f	17	o	o	2	3	10	0	0	0	0	0	1
113	m	11	o	o	2	3	10	0	0	0	8	20	42
114	m	21	o	o	3	13	48	4	0	0	4	32	33
115	m	10	x	x	3	13	44	7	0	0	0	12	25
116	f	30	o	o	3	9	16	12	0	0	20	12	29
117	m	6	o	o	2	3	11	0	0	0	11	23	23
118	f	6	x	o	4	20	36	40	1	0	0	1	0
119	m	6	o	o	3	13	28	22	0	0	18	12	32
120	f	11	o	o	5	3	3	2	1	1	1	13	31
121	m	51	o	o	3	6	20	4	0	0	28	12	35
122	f	14	o	o	3	2	4	4	0	0	1	27	30
123	m	14	o	o	3	2	4	4	0	0	1	0	32
124	f	13	o	o	3	3	4	4	0	0	1	0	29
125	f	12	o	o	4	11	20	16	7	0	28	12	30
126	m	11	o	o	2	1	2	0	0	0	4	0	23
127	m	10	o	o	3	4	14	1	0	0	0	12	20
128	f	4	o	o	2	7	26	0	0	0	0	12	19
129	m	3	o	o	4	9	24	8	3	0	0	0	5
130	m	3	o	o	2	3	4	0	0	0	1	0	17
131	f	8	o	o	2	3	2	0	0	0	0	0	7
132	f	2	o	o	4	59	28	168	36	0	13	12	13
133	m	13	o	o	2	6	23	0	0	0	4	0	4
134	m	14	o	o	4	2	5	1	1	0	1	0	9
135	f	10	o	o	6	15	36	12	4	4	5	0	9
136	m	15	o	o	5	3	2	4	2	2	3	0	6
137	m	14	o	o	2	7	24	0	0	0	4	0	5
138	f	15	o	x	3	2	2	1	0	0	1	0	1
139	f	12	o	o	2	2	5	0	0	0	0	0	1
140	f	3	o	o	5	38	24	4	8	4	0	0	0
141	f	12	o	o	2	11	9	0	0	0	3	0	10
142	m	3	o	o	3	54	200	3	0	0	11	26	32
143	m	10	o	o	2	1	2	0	0	0	1	0	30
144	f	11	o	o	3	16	56	5	0	0	1	20	34
145	m	7	x	o	2	6	24	3	0	0	0	0	7

APPENDIX 6 contd

No	Sex	Age	Legend number.										
			1	2	3	4	5	6	7	8	9	10	12
146	f	5	x	x	2	4	15	0	0	0	1	13	13
147	m	5	o	o	2	5	20	0	0	0	0	12	15
148	f	9	o	o	4	2	2	2	1	0	2	0	11
149	m	7	o	o	3	1	1	1	0	0	0	0	7
150	f	11	o	o	4	39	48	48	36	0	0	0	10
151	f	4	o	x	3	22	84	3	0	0	0	0	7
152	m	5	o	o	2	2	5	0	0	0	0	0	5
153	f	10	o	o	5	9	32	1	1	1	0	0	8
154	m	8	o	o	3	4	1	14	0	0	1	0	6
155	m	13	o	o	3	2	1	4	0	0	1	0	2
156	f	15	o	o	2	4	16	0	0	0	0	0	0
157	m	30	x	x	2	4	2	0	0	0	0	0	0
158	f	22	o	o	2	12	40	0	0	0	0	0	1
159	f	32	o	o	2	5	15	0	0	0	0	0	4
160	f	17	o	o	4	2	2	2	0	0	0	0	8
161	f	30	o	o	2	4	1	0	0	0	0	0	3
162	f	40	o	o	2	3	11	0	0	0	0	0	3
163	m	31	o	o	3	4	10	4	0	0	0	0	6
164	m	26	o	o	2	9	24	0	0	0	8	0	6
165	f	33	o	o	2	9	28	0	0	0	0	0	8
166	f	37	o	x	3	2	1	1	0	0	1	0	2
167	f	49	o	o	2	3	5	0	0	0	0	0	8
168	m	16	o	o	2	8	16	0	0	0	5	0	7
169	f	29	o	o	3	12	28	6	0	0	5	0	11
170	m	18	o	o	6	26	12	4	72	4	0	0	10
171	m	41	o	o	2	6	8	0	0	0	2	0	0
172	f	19	o	o	2	6	22	0	0	0	0	0	12
173	f	19	o	o	6	17	24	4	16	2	0	0	11
174	m	53	o	x	2	1	3	0	0	0	0	0	10
175	f	14	o	o	3	36	76	52	0	0	0	12	12
176	f	11	o	o	2	2	8	0	0	0	0	0	1
177	f	4	o	o	3	5	4	4	0	0	0	0	0
178	m	9	o	o	3	6	5	12	0	0	0	0	5
179	m	15	o	o	2	5	4	0	0	0	1	0	4
180	f	9	o	o	3	2	8	4	0	0	2	0	12
181	f	11	o	o	4	25	16	64	22	0	0	0	3
182	m	5	x	x	3	9	24	8	0	0	0	0	7
183	m	12	o	o	3	4	6	6	0	0	6	0	9

PUBLISHED PAPERS

1. Elwes RDC, Johnson AL, Shorvon SD, Reynolds EH.
The prognosis for seizure control in newly diagnosed epilepsy.
N Eng J Med 1984; 311:944-7.

2. Elwes RDC, Chesterman P, Reynolds EH.
Prognosis after a first untreated tonic-clonic seizure.
Lancet 1985; ii:752-3.

3. Elwes RDC, Johnson AL, Reynolds EH.
The natural history of untreated epilepsy.
Br Med J 1988; in press.

Reprinted from THE LANCET, *October 5, 1985, pp. 752–753*

PROGNOSIS AFTER A FIRST UNTREATED TONIC-CLONIC SEIZURE

R. D. C. ELWES P. CHESTERMAN
E. H. REYNOLDS

Department of Neurology, Institute of Psychiatry and King's College Hospital Medical School, London

Summary The prognosis for seizure recurrence was assessed in 133 patients who presented at a median of 1 day after a first-ever tonic-clonic seizure. The cumulative probability of recurrence was 20% by 1 month, 28% by 2 months, 32% by 3 months, 46% by 6 months, 62% by 1 year, and 71% by 3 and 4 years. After a first seizure epilepsy is likely to develop in the majority of patients.

Introduction

THE patient presenting with a single tonic-clonic seizure is a common clinical problem. Estimates of the cumulative incidence of epilepsy have suggested that as many as 5% of the population will experience at least one afebrile seizure at some time during their life.[1] Little is known, however, about the early prognosis of epilepsy, and opinions on the risk of subsequent seizures after the initial attack have differed (table I).[2–7] Four studies[2,4,6,7] found that about a third of patients who present with a single seizure will have a second, but in other studies the prognosis was worse.[3,5]

Patients and Methods

Between 1978 and 1983, 328 newly referred patients with previously untreated seizures were seen in our neurology outpatient department. In 42 patients the seizures were related to alcohol withdrawal, drugs, acute metabolic disturbance, or fever. 72 patients had myoclonic, petit mal, or partial seizures without

TABLE I—STUDIES OF PROGNOSIS AFTER FIRST TONIC-CLONIC SEIZURE

Ref	n	Recurrence (%)	Mean (range) follow-up (mo)
2	48	27	NK (42–102)
3	77	64	36
4	39	33	26 (10–48)
5	74	56	36
6	70	39	57 (36–120)
7	244	27	22 (6–55)

NK = not known; n = number of patients.

secondary generalisation. Of the 214 patients with tonic-clonic seizures, 133 first presented to medical attention after a single seizure. 73 were seen in accident and emergency departments and 60 by their family practitioner. No patient was treated after the initial seizure. Patients who were seizure-free when discharged were recalled to the clinic in January, 1984, or contacted by letter to assess seizure recurrence. The patient characteristics and follow-up times are summarised in table II.

The aetiology of the seizures was vascular in 7 patients, birth injury in 3, post-traumatic in 3, and brain tumour in 3. 5 of the patients had hemiparesis, 3 cognitive deficits, and 2 other neurological deficits. The cumulative probability of seizure recurrence in 1-month periods was assessed by Kaplan-Meier survival curves.[8]

Results

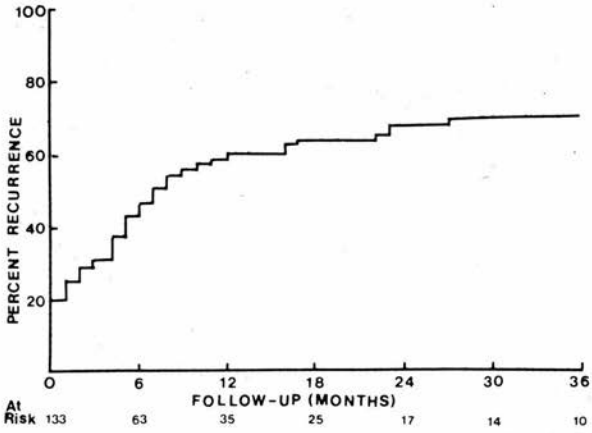
The median time between first seizure and first presentation was 1 day and median follow-up from the time of the first seizure was 15 months. The cumulative probability of seizure recurrence (see figure) was 20% by 1 month, 28% by 2 months, 32% by 3 months, 46% by 6 months, 62% by 1 year, 69% by 2 years, and 71% by 3 and 4 years.

Discussion

Cleland et al[6] found that epilepsy subsequently developed in 39% of patients who presented with an isolated seizure in adult life; a seizure was labelled "isolated" if the patient had not experienced a second attack by the time of first attendance at a neurology outpatient department, some 6 weeks after the event. Two earlier studies,[2,4] both based on patients attending electroencephalography departments, had similar results. However, the time between first and second seizures is likely to be less than a month in at least a third of patients

TABLE II—CHARACTERISTICS AND FOLLOW-UP OF 133 PATIENTS

	Number (%)
Male	70 (53)
Female	63 (47)
Median (range) age at first afebrile seizure (yr)	21 (2–74)
Symptomatic seizures	16 (13)
Neurological deficit	10 (8)
Follow-up (mo)	
1–12	57 (42)
13–24	33 (25)
25–36	17 (13)
37–48	13 (10)
>48	13 (10)
Median (range) follow-up	15 (1–69)



Cumulative probability of seizure recurrence in 133 patients presenting with a single seizure.

with established epilepsy.[9] In our study the recurrence rate was already 28% by the second month of follow-up. At the time of first attendance at a hospital clinic, therefore, a considerable proportion of patients would have been excluded from analysis in these studies[2,4,6] because epilepsy had already developed. Hauser et al[7] studied 244 patients with one unprovoked seizure; the cumulative probability of seizure recurrence was 27% by 36 months. However, 435 patients who had had two or more seizures at first diagnosis were excluded from analysis. Unlike our patients, 69% were treated after the first seizure, which may also have contributed to the low recurrence rate.

We do not know what proportion of patients who experience a single seizure are not referred to hospital. A survey[10] of life-time general-practice records of 6000 patients suggests that it is low; furthermore, of patients with seizures, only a fifth were found to have had a single attack. Our results in patients referred to a neurology outpatient department are similar and support Gowers' statement in 1881 that epilepsy is likely to develop in the majority of patients after a first seizure.[9]

It appears to be the current practice of most neurologists not to treat a single seizure.[11] Livingston[12] has stated that seizures recur in 91% of children without treatment and in only 19% of those given anticonvulsants. Hauser et al[7] found no difference in prognosis between patients treated or

untreated for a single seizure. However, they treated only those patients considered by the referring clinicians to be at high risk of recurrence.[13] Neither report gave details of whether the drugs were taken or monitored. Although the outlook for seizure control in newly diagnosed epilepsy is good,[14] it is possible that immediate treatment after a first seizure might reduce the recurrence rate and improve subsequent prognosis.[15] There has, however, been no adequate investigation of the value or otherwise of treating single seizures.

Correspondence should be addressed to E. H. R., Department of Neurology, King's College Hospital, Denmark Hill, London SE5 9RS.

REFERENCES

1. Hauser WA, Kurland LT. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. *Epilepsia* 1975; **16:** 1–66.
2. Thomas MH. The single seizure: its study and management. *JAMA* 1959; **169:** 457–59.
3. Johnson LC, De Bolt WL, Long MT, et al. Diagnostic factors in adult males following initial seizures: a three year follow-up. *Arch Neurol* 1972; **27:** 193–97.
4. Saunders M, Marshall C. Isolated seizures: an EEG and clinical assessment. *Epilepsia* 1975; **16:** 731–33.
5. Blom S, Heijbel J, Bergfors PG. Incidence of epilepsy in children: a follow-up study three years after the first seizure. *Epilepsia* 1978; **19:** 343–50.
6. Cleland PJ, Mosquera I, Steward WP, Foster JB. Prognosis of isolated seizures in adult life. *Br Med J* 1981; **283:** 1364.
7. Hauser WA, Anderson VE, Lowenson RB, McRoberts SM. Seizure recurrence after a first unprovoked seizure. *N Engl J Med* 1982; **307:** 522–28.
8. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Statist Assoc* 1958; **53:** 457–81.
9. Gowers WR. Epilepsy and other chronic convulsive disorders. London: Churchill, 1881.
10. Goodridge DMG, Shorvon SD. Epileptic seizures in a population of 6000. II: Treatment and prognosis. *Br Med J* 1983; **287:** 645–47.
11. Reynolds EH. The initiation of anticonvulsant drug therapy: implications for prognosis. In: Pedley TA, Meldrum BS, eds. Recent advances in epilepsy. Edinburgh: Churchill Livingstone, 1984: 101–09.
12. Livingston S. Convulsive disorders in infants and children. *Adv Paediatr* 1958; **10:** 113–95.
13. Tucker SH, McJunkin JE. Seizure recurrence. *N Engl J Med* 1984; **311:** 1702.
14. Elwes RDC, Johnson AL, Shorvon SD, Reynolds EH. The prognosis for seizure control in newly diagnosed epilepsy. *N Engl J Med* 1984; **311:** 944–47.
15. Reynolds EH, Elwes RDC, Shorvon SD. Why does epilepsy become intractable? Prevention of chronic epilepsy. *Lancet* 1983; ii: 952–54.

Printed in Great Britain

THE PROGNOSIS FOR SEIZURE CONTROL IN NEWLY DIAGNOSED EPILEPSY

ROBERT D. C. ELWES, M.B., CH.B., ANTHONY L. JOHNSON, PH.D., SIMON D. SHORVON, M.D., AND EDWARD H. REYNOLDS, M.D.

Abstract We assessed the prognosis for seizure control in 106 patients who were referred to an adult neurology clinic with previously untreated tonic–clonic, partial, or mixed seizures and were followed prospectively for a median of 66 months (range, 6 to 96). Twenty-six patients remained completely free of seizures for as long as they were followed. Actuarial analysis showed that 35 per cent of patients could be expected to enter a seizure-free period of at least two years at the start of treatment, 73 per cent would have had a two-year seizure-free period at the end of four years, and 82 per cent would have had a two-year seizure-free period at the end of eight years. Of 79 patients whose seizures were completely controlled for at least two years, 51 subsequently remained seizure-free. If seizures continued for up to two years after the start of treatment, the probability of subsequent seizure control fell by half. The presence of partial seizures; a high frequency of tonic–clonic seizures before treatment; a neurologic, social, or psychiatric handicap; and a family history of epilepsy each indicated a worse prognosis.

We conclude that the long-term pattern of seizure control is largely established during the first two years of treatment. (N Engl J Med 1984; 311:944-7.)

STUDIES of the prognosis for seizure control in epilepsy have given widely conflicting results (Table 1). In an authoritative review Rodin[6] found that if control was defined as complete freedom from all seizures for at least one year, then about two thirds of patients with epilepsy were likely to have a chronic seizure disorder. However, more recent studies have suggested a better prognosis. In a retrospective survey of patients from 20 institutions[9] in whom the outcome for seizure control was assessed up to 10 years after the onset of the illness, 58 per cent were found to have been completely free of seizures for more than three years. Two retrospective community-based sur-

From the University Department of Neurology, Institute of Psychiatry and King's College Hospital Medical School, London, and the MRC Biostatistics Unit, Medical Research Council Centre, Cambridge, England. Address reprint requests to Dr. Reynolds at the Department of Neurology, King's College Hospital, Denmark Hill, London SE5 9RS, England.

Supported in part by the Medical Research Council, Ciba–Geigy, Parke–Davis, Labaz, and the British United Provident Association.

Reprinted from *The New England Journal of Medicine*
311:944-947 (October 11), 1984

Table 1. Studies of the Prognosis for Seizure Control in Patients with Epilepsy.

Study	No. of Patients	Seizure-Free Period (Yr)	% Seizure-Free
Alstrom, 1950[1]	897	3	22
Strobos, 1959[2]	228	2	38
Kiorboe, 1960[3]	130	4	32
Trolle, 1960[4]	799	2	37
Juul-Jensen, 1963[5]	969	2	32
Rodin, 1968[6]	90	2	32
Currie et al., 1971[7] *	666	1	40
Annegers et al., 1979[8] †	457	5	70
Okuma & Kumashiro, 1981[9]	1868	3	58
Goodridge & Shorvon, 1983[10] †	122	4	69

*Temporal-lobe epilepsy only.
†Community surveys.

veys[8,10] showed that the prognosis for about three quarters of patients was good.

There are many difficulties in interpreting these apparently conflicting results. Definitions of remission, durations of follow-up and classifications of seizures have differed. None of the studies used a consistent treatment plan with extensive monitoring of serum anticonvulsant levels throughout follow-up to assess either optimal use of medication or poor compliance.

The greatest problem, however, has been patient selection. Epilepsy is a disorder with a widely varying outcome, and hospital clinics tend to accumulate patients with chronic intractable seizures. Previous hospital-based studies have used a cross-sectional sample of patients. The prognosis in chronic epilepsy is probably very poor,[11] and inclusion of patients with chronic disease could well account for much of the disagreement. We performed a prognostic study in previously untreated patients who were newly referred for epilepsy and followed for up to eight years.

Methods

Between 1974 and 1979, 106 consecutively referred patients attending the Adult Neurology Clinic at King's College Hospital, London, were entered into the study. Each patient had had two or more tonic–clonic or partial seizures (or both) in the previous year. Patients with seizures induced by alcohol, metabolic abnormalities, or drugs and those with a progressive neurologic disorder at diagnosis were excluded. Seizures were classified clinically in accordance with the international classification.[12] The clinical characteristics and follow-up intervals are summarized in Table 2. A family history of epilepsy was defined as epilepsy in first degree or second-degree relatives. The frequency of tonic–clonic seizures before treatment was assessed in 79 patients with tonic–clonic seizures alone or with mixed seizure types. A high seizure frequency was defined as two or more seizures a month. A neurologic handicap was defined as the presence of focal neurologic signs, mental retardation, or an unequivocal abnormality on a CT scan; a psychiatric or social handicap was defined as a problem of sufficient severity to warrant referral to a psychiatrist or social worker.

Sixty-one patients were treated with phenytoin, and 45 with carbamazepine. Serum levels of anticonvulsants were monitored, and if seizures continued the dosage was increased until they were controlled. The occurrence of two or more seizures despite an optimal serum level of anticonvulsant was taken as evidence of failure of single-drug therapy. The treatment methods and responses to single-drug therapy in 94 patients after a median interval of 32 months have been reported previously.[13] Two patients with drug-induced skin rashes, two with tumors developing during treatment, and eight who were lost to follow-up are included in the present analysis.

Statistical Analysis

The follow-up period was divided into two-month intervals, and patients were designated as being with or without tonic–clonic or partial seizures for each interval. Kaplan–Meier survival curves[14] were used to analyze the percentages of patients who were completely free of seizures for one- and two-year periods. Significance values are based on the log-rank test.[15] The percentages shown in the figures are actuarial.

Results

At completion of the study, eight patients had been lost to follow-up after a median interval of 1.9 years. Of the remaining 98 patients, 62 were still taking their original drug, 18 had successfully stopped taking medication, and 18 had changed their treatment. Treatment failed in 21 patients — by one year in 13, by two years in a total of 19, and by six years in another 2.

Twenty-six patients remained completely free of seizures for a median follow-up period of 64 months after the beginning of anticonvulsant treatment. Among the 80 patients who had a recurrence of seizures, 35 had a

Table 2. Characteristics of the 106 Patients Entered in the Study.

Feature	No. (%) *	Actuarial % Seizure-Free for One Year		
		at 1 yr	at 2 yr	at 5 yr
Sex				
Male	51 (48)			
Female	55 (52)			
Median age at diagnosis — yr	23 (range, 6–77)			
Months of follow-up				
<24	5 (5)			
25–48	14 (13)			
49–72	48 (45)			
73–96	39 (37)			
Median follow-up — mo	66 (range, 6–96)			
Seizure type				
Tonic–clonic alone	59 (55)	46	83	97
Partial alone	22 (21)	23	54	73
Mixed	25 (24)	38	66	89
Family history of seizures				
Present	22 (21)	37	51	73
Absent	84 (79)	40	79	93
Pretreatment frequency of of tonic–clonic seizures				
High	45 (57)	36	74	93
Low	34 (43)	56	88	100
Neurologic handicap				
Present	35 (33)	26	62	84
Absent	71 (67)	46	78	92
Social handicap				
Present	27 (25)	11	54	74
Absent	79 (75)	48	79	95
Psychiatric handicap				
Present	31 (29)	20	68	79
Absent	75 (71)	47	75	93
Total	106 (100)	40	73	89

*Figures are numbers and percentages of patients except where otherwise indicated. See text for definitions.

recurrence by two months, 44 by four months, 51 by six months, and 62 by one year. One patient was seizure-free and lost to follow-up at six months. Twelve patients had seizures that could all be related to poor compliance with medication.

The actuarial percentage of patients with complete suppression of all seizures for periods of one and two years is shown by duration of follow-up in Figure 1. A one-year seizure-free period occurred in 40 per cent by one year, 73 per cent by two years, 84 per cent by three years, 88 per cent by four years, 89 per cent by five years, and 92 per cent by eight years. The pattern for two-year seizure-free periods was similar, occurring in 35 per cent by two years, 57 per cent by three years, 73 per cent by four years, 79 per cent by five years, and 82 per cent by eight years. There were 79 patients in whom seizures were controlled for two years, and subsequent follow-up data were available in 76. Fifty-one remained completely seizure-free for the rest of follow-up. Twenty-five had a recurrence of seizures, which consisted of one or two attacks in 17 and was related to poor compliance in 16.

Factors of prognostic importance were investigated by analysis of the actuarial percentage of patients who were completely seizure-free for one year (Table 2). The presence of partial seizures (log-rank statistic: $\chi^2 = 9.1$, d.f. = 2, P = 0.011); a family history of epilepsy ($\chi^2 = 5.4$, d.f. = 1, P = 0.02); a high frequency of tonic–clonic seizures before treatment ($\chi^2 = 5.3$, d.f. = 1, P = 0.022); or a neurologic ($\chi^2 = 3.8$, d.f. = 1, P = 0.05), social ($\chi^2 = 11.6$, d.f. = 1, P<0.001), or psychiatric handicap ($\chi^2 = 4.3$, d.f. = 1, P = 0.038) predicted a worse prognosis. Age at onset of seizures; number of tonic–clonic seizures before treatment; nocturnal or diurnal timing of seizures; and the presence of epileptic, focal, or background abnormalities on the pretreatment electroencephalogram were not of prognostic value.

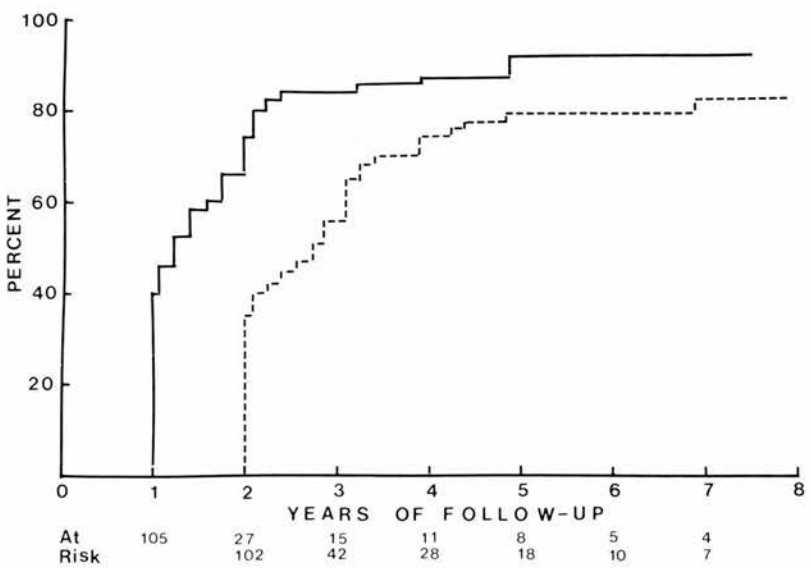


Figure 1. Actuarial Percentage of Patients Completely Free of Seizures for One Year (Solid Lines) and Two Years (Broken Lines).

The influence of early response to treatment on subsequent seizure control was also assessed (Fig. 2). Ninety-two per cent of all patients had a one-year period in which they were completely seizure-free. In 63 patients who had seizures during the first year of treatment, 77 per cent were controlled, and in 32 who continued to have seizures during the second year, 57 per cent were controlled. If seizures continued for up to two years after the start of treatment, the probability of a subsequent one-year period completely free of seizures had fallen by about half.

Discussion

In this prolonged prospective follow-up study of newly diagnosed epileptic patients, the outlook for seizure control was good. Twenty-six patients remained completely free of seizures for a median follow-up period of 64 months, and 82 per cent had a two-year period in which they were completely seizure-free. These findings contrast sharply with those of previous hospital-based studies,[6] which have shown that about two thirds of patients with epilepsy are likely to have a chronic seizure disorder.

The most important explanation for the good prognosis in our patients is that we followed them from the time of diagnosis and therefore avoided the selection bias of previous cross-sectional studies, all of which included patients with chronic epilepsy. Our study also differed from previous ones in that a consistent pattern of treatment was maintained throughout follow-up, with extensive use of serum anticonvulsant monitoring. In patients who took their prescribed medication, treatment was therefore optimized, and this may have contributed to the good prognosis.

The suggestion that the prognosis in epilepsy is far better than previous hospital-based studies have shown is strongly supported by epidemiologic and community-based surveys. Although more than 5 per cent of the population have at least one afebrile seizure at some time during their lives,[16] the prevalence rates for active epilepsy are on the order of 4 to 6 per thousand,[17] suggesting that remissions occur in many patients. Two recent retrospective community-based surveys have supported this suggestion.[8,10] In both surveys about three quarters of patients entered a prolonged seizure-free period, and the prognosis improved with increasing time after diagnosis.

Partial seizures; a high frequency of tonic–clonic seizures before treatment; a neurologic, social, or psychiatric handicap; and a family history of epilepsy were each associated with a poorer prognosis for seizure control. These factors have also been associated with a poorer prognosis in chronic epilepsy,[6] re-

lapse on attempted withdrawal of anticonvulsants,[18] and seizure recurrence after a single seizure.[19] Characteristics of the pretreatment electroencephalogram and age at onset of seizures were not associated with prognosis.

The longer seizures continued after the start of treatment, the less likely was control. If seizures were continuing after two years of treatment, the probability of ever achieving a one-year seizure-free period had fallen by half. Since all patients were treated it is impossible to tell whether this reflects the natural history of the disorder or whether early control may indeed affect long-term prognosis. Evidence for this possibility could only be obtained from a randomized study involving an untreated control group. Little is known about the natural history of untreated epilepsy. Gowers stated over a century ago that "spontaneous cessation of the disease is an event too rare to be reasonably anticipated in any given case."[20] His career spanned the period when bromides (probably the first effective treatment for epilepsy) were introduced, and he thought the drugs had a major impact. He also suggested that seizures might be self-promoting, each one predisposing to the next. It is possible, therefore, that anticonvulsants not only suppress seizures but actually alter the natural history of the disorder.

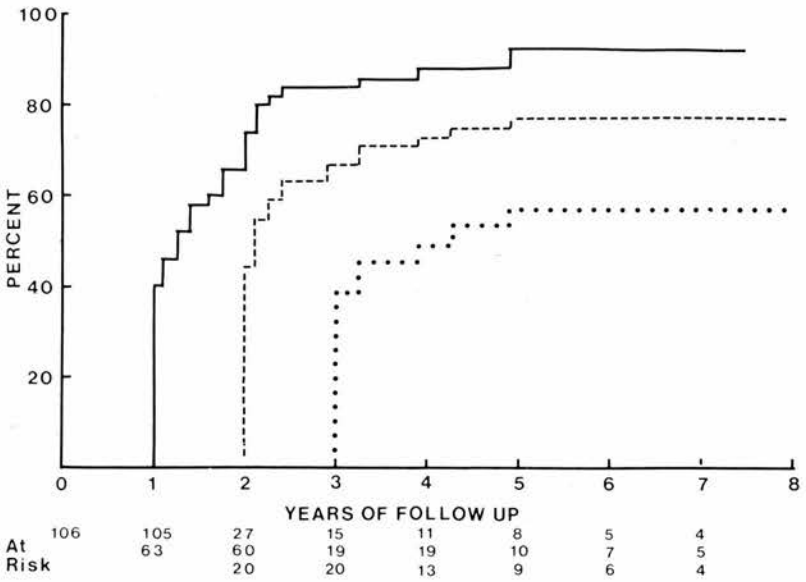


Figure 2. Influence of Duration of Seizures on Actuarial Percentage of Patients Completely Free of Seizures for One Year.

Solid lines represent all patients from start of treatment, broken lines patients with seizures in the first year of follow-up, and dots patients with seizures in the first two years of follow-up.

Although the overall outlook for seizure control is good, about a quarter of patients do not respond to the initial drug used, and our experience has been that the disorder in most of these patients is not subsequently controlled despite additions or changes in medication.[21] These patients are treated in hospital or specialized epilepsy clinics for chronic intractable epilepsy, and because of the high prevalence of the disorder, they present a major management problem, using most of the available resources for the treatment of epilepsy. The pattern of seizure control, however, is established within the first one or two years. This, surprisingly, is an area of research that has been largely neglected. Further study is needed to establish whether more effective treatment at the onset of seizures may prevent the development of chronic intractable epilepsy.[22]

We are indebted to Drs. S. Brown, D. Chadwick, C. Dellaportas, A. Galbraith, and M. McGowan for clinical assistance.

References

1. Alström CH. A study of epilepsy in its clinical, social and genetic aspects. Acta Psychiatr Neurol Scand [Suppl] 1950; 63:1-284.
2. Strobos RRJ. Prognosis in convulsive disorders. Arch Neurol 1959; 1: 216-25.
3. Kiørboe E. The prognosis of epilepsy. Acta Psychiatr Neurol Scand [Suppl] 1961; 150:166-78.
4. Trolle E. Drug therapy of epilepsy. Acta Psychiatr Neurol Scand [Suppl] 1960; 150:187-99.
5. Juul-Jensen P. Epilepsy: a clinical and social analysis of 1020 adult patients with epileptic seizures. Copenhagen: Munksgaard, 1963.
6. Rodin EA. The prognosis of patients with epilepsy. Springfield, Ill.: Charles C Thomas, 1968.
7. Currie S, Heathfield KWG, Henson RA, Scott DF. Clinical course and prognosis of temporal lobe epilepsy: a survey of 666 patients. Brain 1971; 94:173-90.
8. Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. Epilepsia 1979; 20:729-37.
9. Group for the Study of Prognosis of Epilepsy in Japan. Natural history and prognosis of epilepsy: report of a multi-institutional study in Japan. Epilepsia 1981; 22:35-53.
10. Goodridge DGM, Shorvon SD. Epileptic seizures in a population of 6000. II. Treatment and prognosis. Br Med J 1983; 287:645-7.
11. Rodin E, Klutke G, Chayasirisobohn S. Epileptic patients who are refractory to anticonvulsant medications. Neurology (NY) 1982; 32:1382-4.
12. Gastaut H. Clinical and electroencephalographical classification of epileptic seizures. Epilepsia 1970; 11:102-13.
13. Shorvon SD, Reynolds EH. Early prognosis of epilepsy. Br Med J 1982; 285:1699-701.
14. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-81.
15. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977; 35:1-39.
16. Hauser WA, Kurland LT. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. Epilepsia 1975; 16:1-66.
17. Zielinsky JJ. Epidemiology. In: Laidlaw J, Richens A, eds. A textbook of epilepsy. 2nd ed. Edinburgh: Churchill Livingstone, 1982:16-33.
18. Oller-Daurella L, Pamies R, Oller L. Reduction or discontinuance of antiepileptic drugs in patients seizure-free for more than five years. In: Janz D, ed. Epileptology: proceedings of the seventh International Symposium on Epilepsy Berlin (West), June 1975. Stuttgart: Georg Thieme, 1976:218-27.
19. Hauser WA, Anderson VE, Loewenson RB, McRoberts SM. Seizure recurrence after a first unprovoked seizure. N Engl J Med 1982; 307:522-8.
20. Gowers WR. Epilepsy and other chronic convulsive disorders: their causes, symptoms, and treatment. London: Churchill, 1881.
21. Elwes RDC, Johnson AL, Shorvon SD, Reynolds EH. The early prognosis of epilepsy. In: Parsonage M, Grant RHE, Craig AG, Ward AA, eds. Advances in epileptology: the 14th Epilepsy International Symposium. New York: Raven Press, 1983:133-41.
22. Reynolds EH, Elwes RDC, Shorvon SD. Why does epilepsy become intractable?: prevention of chronic epilepsy. Lancet 1983; 2:952-4.